Semi-Annual Meeting, St. Louis, Missouri, November 29-30, 1953

VOLUME XXIV NUMBER 4

DISEASES

of the

CHEST

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AMERICAN COLLEGE OF CHEST PHYSICIANS

René Laënnec

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1. Kaufman and Farmer (1951), Ann. Allergy, 9:89, January-February
2. Swartz (1950), Ann. Allergy, 8:488, July-August
3. Krasno et al. (1949), J. Allergy, 20:111, March

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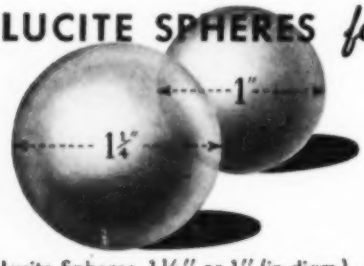

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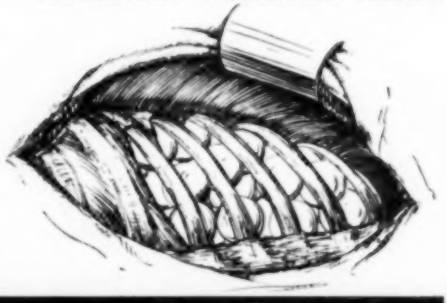

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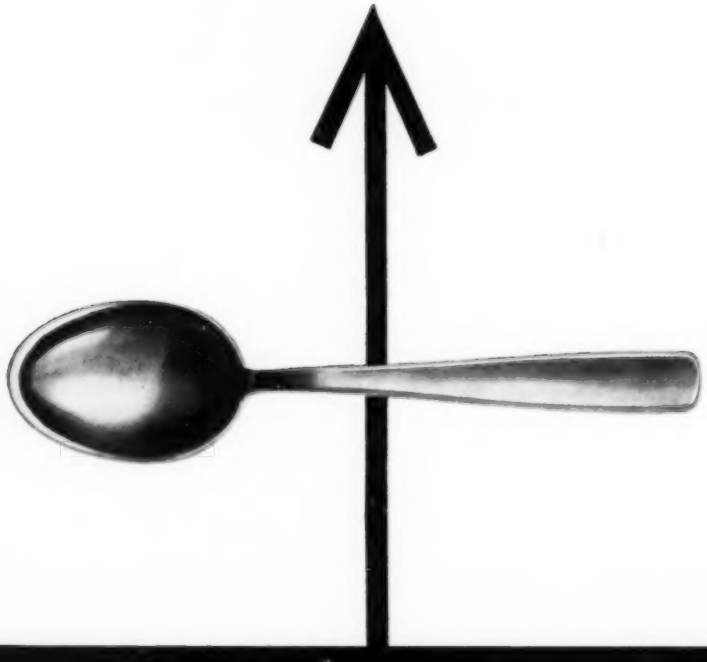

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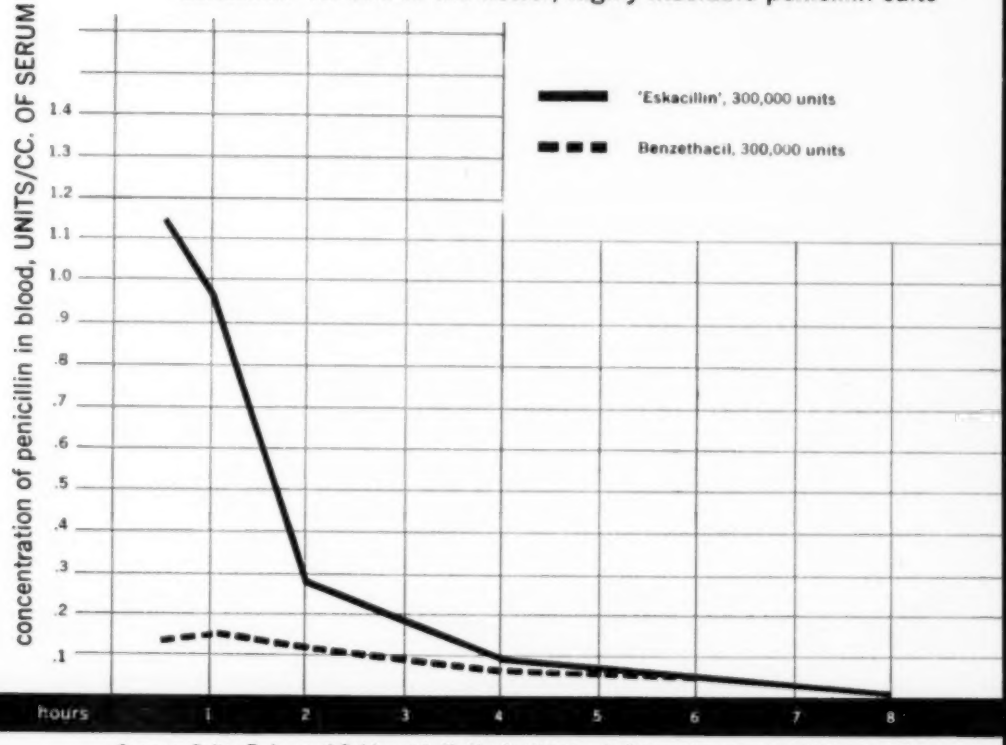

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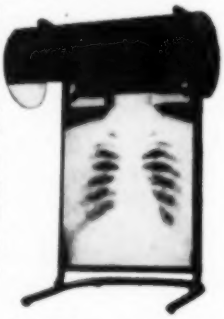

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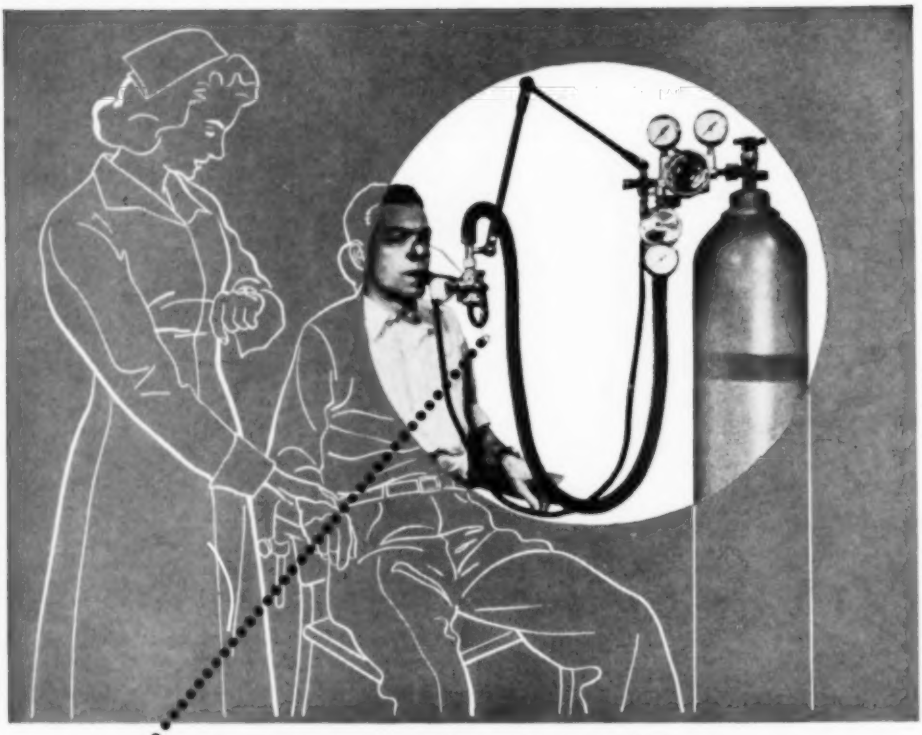

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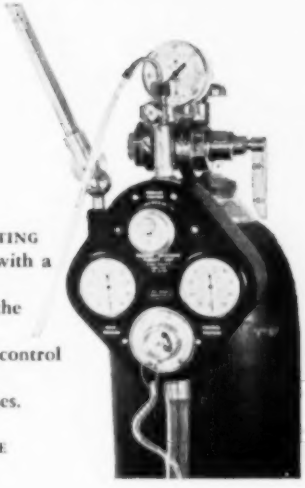

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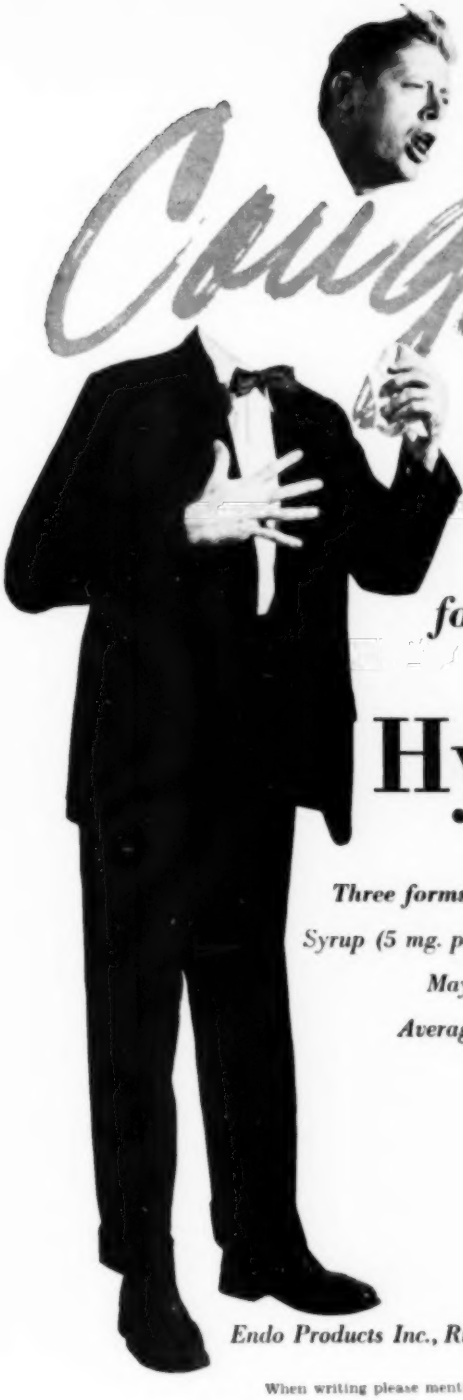

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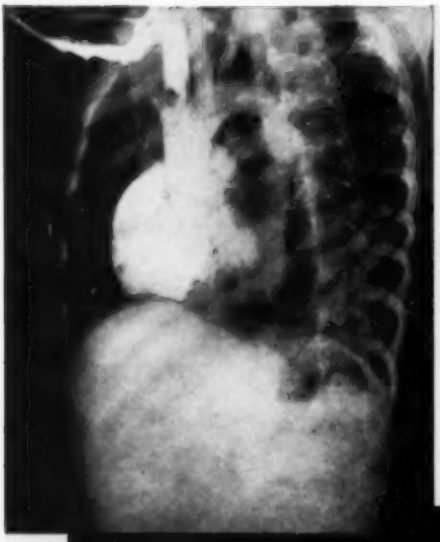

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1. Meakins, J. C.: The Practice of Medicine, ed. 5, St. Louis, The C. V. Mosby Company, 1950, p. 154.
2. *Ibid.*, p. 268.
3. Bishop, P. A., and Lindskog, G. E.: Lung Abscess, in Pillmore, G. U.: Clinical Radiology, Philadelphia, F. A. Davis Company, 1950, vol. 1, p. 339.

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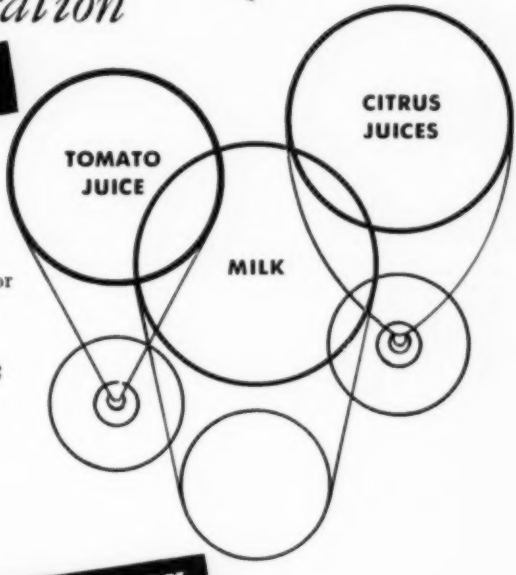

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1. Hobby, G. L., Lenert, T. F., Rivoire, Z. C., Donikian, M., and Fikula, D.: Am. Rev. Tuberc. 67:808, 1953.

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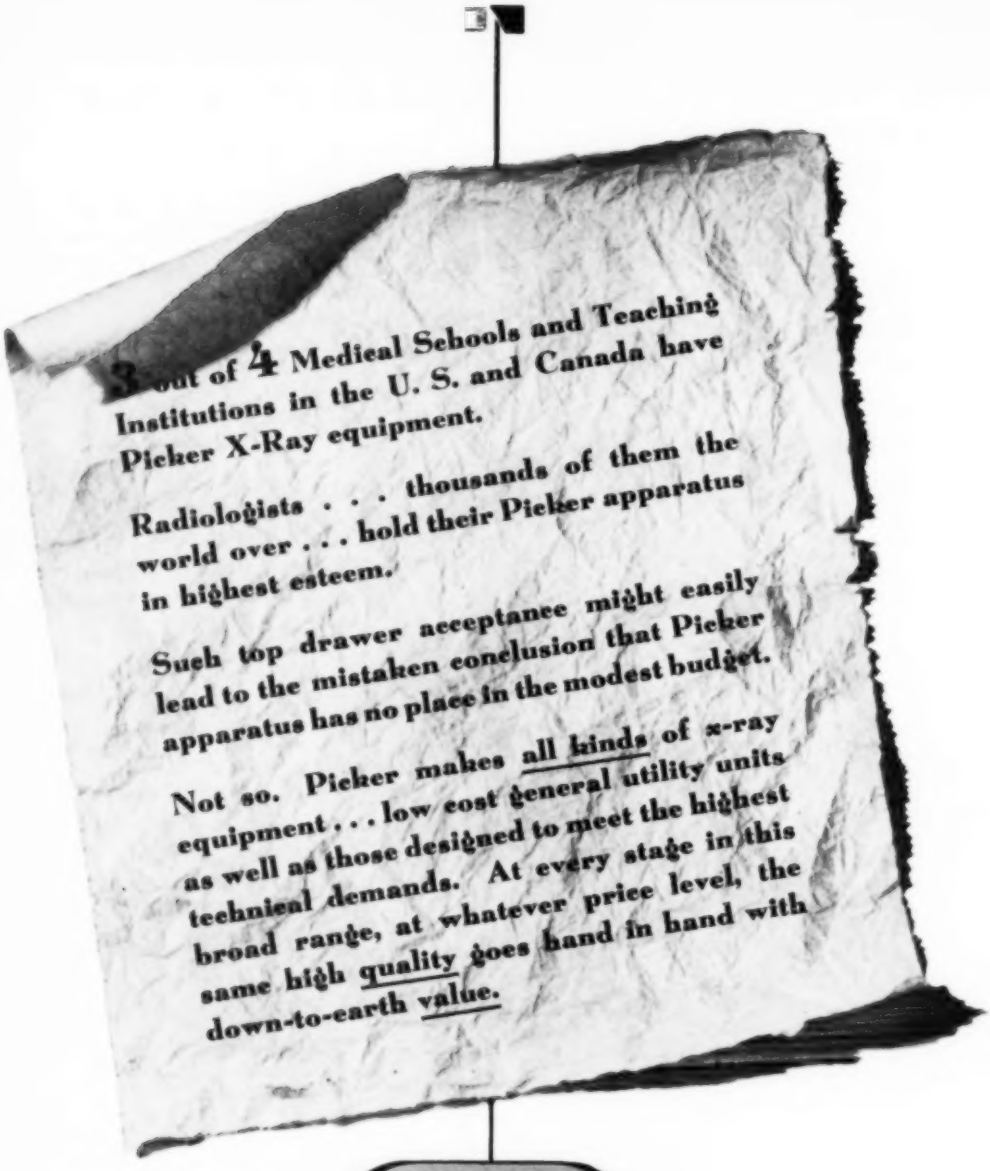
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DISEASES *of the* CHEST

VOLUME XXIV OCTOBER 1953 NUMBER 4

Control Study of Isoniazid: Factors Influencing the Response of Pulmonary Tuberculosis to Chemotherapy

A United States Public Health Service Cooperative Investigation*

The announcement early in 1952 of the remarkable results achieved in the first trials of isoniazid in tuberculous patients was followed by widespread uncertainty among physicians throughout the country how best to incorporate the new drug into current treatment programs. Their questions were principally whether isoniazid was as effective as streptomycin plus para-aminosalicylic acid (PAS) and how frequently they could expect in their patients results similar to those obtained in the pilot trials.

To meet this need, the U. S. Public Health Service in April, 1952, invited physicians in 22 tuberculosis hospitals** to undertake a large scale control study of isoniazid.† The hospitals, widely scattered geographically, are representative of the institutions in the United States which give treatment to the civilian population. The patients differ in age, race, sex, economic status, social level, kind of disease and many other characteristics, and represent a cross section of the patients in civilian tuberculosis hospitals. While the clinical investigators are far from being of one mind on how pulmonary tuberculosis can best be treated, they are agreed on the necessity of a control study for the proper evaluation of isoniazid. They have voluntarily imposed upon themselves the few but critical restrictions which a

*Report prepared for the investigators by Shirley Ferebee and presented by Dr. Rufus Payne at the annual meeting of the American College of Chest Physicians, New York City, May, 1953.

**Drs. F. H. Alley, E. P. Bowerman, and S. C. Carter, Tennessee State Tuberculosis sanatoriums at Memphis and Oakville, Tenn.; Dr. P. T. Chapman, Herman Kiefer Hospital, Detroit, Mich.; Dr. S. S. Cohen, Glen Lake Sanatorium, Oak Terrace, Minn.; Dr. H. G. Curtis, Sunny Acres Tuberculosis Hospital, Cleveland, Ohio; Dr. R. J. Davies, Firland Sanatorium, Seattle, Wash.; Dr. F. P. Dawson, Middlesex County Sanatorium, Waltham, Mass.; Dr. Raymond Hofstra, USPHS Hospital, Brooklyn, N. Y.; Drs. W. L. Howard and W. J. Steininger, Maybury Sanatorium, Northville, Mich.; Dr. G. E. Martin, Pittsburgh Tuberculosis Hospital, Pittsburgh, Pa.; Dr. H. M. Payne, Freedmen's Hospital, Washington, D. C.; Drs. R. F. Payne and R. F. Corpe, Battey State Hospital, Rome, Georgia; Drs. Alfred Goldman, Bernard Friedman, and M. B. Pianetto, Robert Koch Hospital, Koch, Mo.; Drs. H. C. Sweany, B. L. Brock, and W. L. Potts, Florida State sanatoriums at Orlando and Lantana, Fla.; Drs. H. S. Willis, H. F. Easom, W. H. Gentry, and C. D. Thomas, North Carolina State sanatoriums at Wilson, McCain, and Black Mountain, N. C.; Dr. G. C. Wilson, Uncas-on-Thames Sanatorium, Norwich, Conn.; and Drs. J. L. Wilson, H. C. Dooling, G. M. Eckley, and H. W. Weest, Pennsylvania State sanatoriums at South Mountain, Cresson, and Hamburg, Pennsylvania.

†The isoniazid for this investigation was generously supplied by E. R. Equibb & Sons as Nydrazid.

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control study involves. The goal has been a diversified group of patients studied objectively in numbers large enough to give in a fairly short period a reliable prediction of what may be generally expected of isoniazid. The present report presents some preliminary results from this study.

Materials and Methods

Background of the study:

During each week from mid-April through August, 1952, the participating hospitals selected patients suitable for the study. According to a list of random numbers prepared for each hospital and held in the central coordinating office,* each patient was assigned to one of the three following regimens: isoniazid alone, isoniazid plus streptomycin, and streptomycin plus PAS. Isoniazid was given in dosages of 150 to 300 mg. daily, streptomycin 1 gm. twice a week, and PAS 10 to 12 gm. daily. The protocol provided for a 64-week period of observation: a 40-week control period, during which only the chemotherapy determined by chance was to be used; and a 24-week post-treatment observation period. In conjunction with the chemotherapy determined by chance, each patient receives whatever other treatment or surgical procedures his condition requires. This provision makes possible comparison of three drug regimens each in combination with the current armamentarium available for the treatment of tuberculosis. Uniform procedures are followed in making and recording clinical and laboratory observations. The current status of each case is reported every four weeks to the central office, where the material is assembled and analyzed by the medical and statistical staff. By September, 1952, 1,500 cases were under observation.

For the purpose of obtaining uniformity in the determination of the drug sensitivity of the tubercle bacilli, arrangements were made to have cultures from all of the 22 cooperating hospitals tested in a single central laboratory (the Trudeau Laboratory, under the supervision of Mr. William Steenken, Jr.).

Approximately three-fourths of the patients had streptomycin-sensitive organisms when they entered the study. The results of treatment in patients who had streptomycin-resistant organisms will be the subject of a later report. At the time this preliminary report was prepared, 791 of the streptomycin-sensitive patients had entered the study early enough to have been observed for the entire 40 weeks of treatment. For a variety of reasons, however, observation or treatment of 208 of the 791 did not follow the original plan. As shown in the text table below, patients who left the hospital against advice make up the largest group. Toxicity severe enough to require discontinuing treatment occurred in six isoniazid cases, 10 streptomycin plus isoniazid cases and 11 streptomycin plus PAS cases. While patients who did not complete treatment must be carefully studied in evaluating the three drug regimens, their analysis falls outside the scope of the present preliminary report.

There remain 583 patients with streptomycin-susceptible infections who

*Located in the Field Research Branch, Div. of Chronic Disease and Tuberculosis.

Reason for Exclusion	Total	REGIMEN		
		Isoniazid	Isoniazid-Streptomycin	Streptomycin-PAS
All reasons	208	64	62	82
Left hospital	153	47	45	61
Change in therapy:				
Refused	7	1	1	5
Drug intolerance	27	6	10	11
Critical worsening	9	5	—	4
Error	8	5	2	1
Non-tuberculous deaths	4	—	4	—

completed 40 weeks of treatment under the protocol. This total includes 205 patients who received isoniazid, 195 isoniazid plus streptomycin, and 183 streptomycin plus PAS.

The assignment of drug regimen to a large number of cases by a system of random numbers was intended to produce three initially comparable groups of patients for the evaluation of the three regimens. The similarity of the composition of the three groups with respect to a number of factors as shown in Table I attests to the success of the randomization.

The present report will be confined chiefly to an analysis of the x-ray film changes occurring during 40 weeks of treatment on the three regimens. Interim results on this study reported elsewhere have given the details of the clinical and bacteriological changes and have shown isoniazid plus streptomycin slightly more effective than the other two regimens, which were approximately equal.

In a typical group of tuberculous patients, only some will have any particular clinical sign, a positive sputum, a productive cough, loss of weight, or elevated temperature. But a pulmonary lesion revealed by x-ray film is the *one* abnormal finding common to *all* tuberculous patients, and change seen on successive x-ray films is generally regarded as one of the most sensitive measures of the effect of treatment. Changes in the serial x-ray films on the patients in this study have been evaluated at periodic conferences of the clinical investigators, and rigorous precautions have been taken to produce objective data on x-ray film change. A system of random allocation of cases to "readers" provided that: each case was reviewed independently by three readers; no physician evaluated any cases from his own hospital; each reader reviewed an equal number of cases in each treatment group and did not know the identity of the patient, the hospital, or the treatment regimen.

For each patient, each of the films taken at four week intervals during treatment was compared with the film taken just before treatment started. Change from the pretreatment film was recorded on a seven-point scale, three degrees of improvement, no change, and three degrees of deterioration. For the present paper, the three independent opinions of the change observable on each film have been consolidated into a majority opinion. On

most films, at least two of the three readers agreed on the exact degree of change; when, for a few films, all three opinions were different, the opinion of the "middle man" on the scale was used.

The material in Table II and Figure 1 is derived from the fourth x-ray film evaluation conference of the clinical investigators held in Washington in April, 1953. Table II shows for each four-week period during the 40 weeks of treatment the distribution of the cases on each regimen over the seven-

TABLE I

Characteristics at Beginning of Study of 583 Patients With Streptomycin-Susceptible Infections.

		PER CENT OF GROUP		
		Isoniazid	Isoniazid-Streptomycin	Streptomycin-PAS
Race	White	62.4	64.6	60.7
	Non-white	37.6	35.4	39.3
Sex	Male	60.0	63.6	59.0
	Female	40.0	36.4	41.0
Age	14-24 years	16.6	13.8	18.0
	25-34 years	23.9	26.2	14.8
	35-44 years	18.0	20.5	25.7
	45-54 years	17.6	15.9	22.4
	55 years and over	23.9	23.6	19.1
Length of present hospitalization	Less than 3 months	52.2	48.2	50.8
	3-5 months	10.7	11.8	12.0
	6-11 months	16.1	17.4	13.1
	1 year or more	21.0	22.6	24.1
Duration of disease	Less than 1 year	43.9	40.0	43.7
	1-2 years	21.5	24.6	22.4
	2-5 years	16.1	13.9	21.9
	Over 5 years	18.5	21.5	12.0
Stage of disease	Minimal	3.9	4.1	5.5
	Moderately advanced	29.3	26.7	21.8
	Far advanced	66.8	69.2	72.7
Temperature	Afebrile	72.2	70.2	71.6
	Slightly febrile	18.5	23.6	22.9
	Markedly febrile	9.3	6.2	5.5
Body weight	Normal or overweight	44.8	50.0	52.5
	Underweight	55.2	50.0	47.5
Amount of sputum	None	6.8	4.6	2.7
	Moderate	72.7	74.9	74.9
	Copious	20.5	20.5	22.4
Cavitation	No cavity	34.1	37.4	37.7
	Single cavity	14.2	10.8	13.1
	Multiple small cavities	28.3	23.6	20.8
	Multiple large cavities	23.4	28.2	28.4
Sputum culture	Negative	28.3	30.3	26.2
	Positive	71.7	69.7	73.8

point scale of x-ray film change, with deaths as an eighth category. In Figure 1, a different shading has been used for each of four categories which are identified in the right hand margin by a symbol: marked improvement (+3), moderate improvement (+2), slight improvement (+1), and no change (0). Deaths and the three degrees of deterioration have been combined, identified by the symbol (−), and shown in black at the top of each illustration in Figure 1.

After 40 weeks of treatment, only 13 patients, or 2 per cent of the 583 patients, had died of tuberculosis: four of them had received isoniazid, four isoniazid plus streptomycin, and five streptomycin plus PAS. Those who became worse under treatment also make up only a small proportion of each group, and, even when combined with deaths, the percentages after 40 weeks of treatment are only 8 per cent among isoniazid patients, 5 per cent among isoniazid-streptomycin patients, and 7 per cent among those treated with streptomycin plus PAS.

Despite 40 weeks of chemotherapy, no change was noted in the x-ray films of slightly more than a fifth of the patients on each regimen, 23 per cent on isoniazid, 21 per cent on isoniazid-streptomycin, and 25 per cent on streptomycin-PAS.

The number of patients showing at least slight improvement increased steadily through 12 weeks of treatment with isoniazid and with isoniazid-streptomycin, and through 20 weeks of streptomycin-PAS. After these peaks, however, few additional patients moved from the "no change" category into the "improved" classifications, and the principal movements thereafter were from the slight improvement into the moderate and marked improvement categories.

In Figure 2, the two categories, marked improvement (+3) and moderate improvement (+2), have been combined and are considered here and throughout the remainder of the report as "significant" x-ray film improvement. It may be seen that these three curves are identical with the upper boundaries of the moderate improvement (+2) category in each of the three illustrations in Figure 1. The purpose of this figure is only to simplify visual comparison of three regimens. Throughout treatment, isoniazid-streptomycin shows a small but consistent superiority, while no difference is apparent between streptomycin-PAS and isoniazid alone. By the 40th week, 56 per cent of the isoniazid-streptomycin group and 46 per cent of both the streptomycin-PAS patients and the isoniazid patients had shown significant x-ray film improvement.

Throughout treatment, the observed differences between the three drug regimens were small and consistent. But on each regimen, the response to treatment ranged from marked improvement to death. The differences among the three regimens were conspicuously less than the differences among patients receiving the same drug. The possibility that the response to chemotherapy is determined by factors other than the choice of drug regimen prompted an examination of the entire group without regard to drug regimen. In the following analysis, the 583 patients have been classified according to three characteristics of the patient: his age, race, and sex;

TABLE II: Percentage Distribution of X-ray Film Change During Treatment in Patients on Three Drug Regimens, Isoniazid, Isoniazid Plus Streptomycin, and Streptomycin Plus PAS

Degree of X-ray Change	WEEKS OF TREATMENT: 4	8	12	16	20	24	28	32	36	40
Isoniazid — 205 patients:										
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Improvement:										
Marked (+3)	—	—	0.5	2.9	4.4	7.8	9.8	12.7	17.2	21.6
Moderate (+2)	2.0	5.4	9.3	19.0	26.3	30.8	33.1	30.7	27.9	24.5
Slight (+1)	20.0	40.0	51.2	42.0	37.1	30.2	26.8	24.4	23.6	23.0
No change (0)	76.5	52.6	34.6	32.6	27.8	25.4	24.9	24.4	22.5	23.0
Deterioration:										
Slight (−1)	1.0	1.0	3.4	2.0	2.4	2.9	1.0	2.9	2.9	2.0
Moderate (−2)	—	0.5	0.5	1.0	1.0	2.4	2.9	3.4	3.9	3.4
Marked (−3)	—	—	—	—	0.5	—	0.5	0.5	0.5	0.5
Death	0.5	0.5	0.5	0.5	0.5	0.5	1.0	1.0	1.5	2.0
Isoniazid Plus Streptomycin — 195 patients:										
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Improvement:										
Marked (+3)	—	0.5	1.5	5.1	8.7	13.3	17.4	20.6	24.1	28.7
Moderate (+2)	2.6	10.3	18.5	30.7	33.3	32.4	31.2	31.7	28.7	27.2
Slight (+1)	21.0	36.9	42.1	30.3	26.7	26.2	22.6	17.4	19.5	18.5
No change (0)	75.9	50.8	36.4	31.3	28.3	22.5	22.1	24.1	22.1	20.5
Deterioration:										
Slight (−1)	—	1.5	1.5	2.1	1.5	2.6	2.6	2.1	1.5	1.5
Moderate (−2)	0.5	—	—	—	0.5	1.5	1.5	1.5	1.5	1.0
Marked (−3)	—	—	—	—	—	—	0.5	0.5	0.5	0.5
Death	—	—	—	0.5	1.0	1.5	2.1	2.1	2.1	2.1

TABLE II: Continued

Degree of X-ray Change	WEEKS OF TREATMENT: 4	8	12	16	20	24	28	32	36	40
Streptomycin Plus PAS — 183 patients:										
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0
Improvement:										
Marked (+3)	—	—	0.5	2.2	5.5	5.5	10.9	13.1	16.4	20.2
Moderate (+2)	1.1	4.9	11.5	17.5	23.0	26.8	30.1	30.6	28.4	25.2
Slight (+1)	19.1	33.9	38.3	38.9	38.9	33.9	26.8	25.2	24.0	22.4
No change (0)	78.2	56.3	44.8	36.6	27.3	27.9	26.3	25.7	24.2	25.2
Deterioration:										
Slight (−1)	1.6	3.3	2.2	1.6	2.7	3.3	2.7	2.2	2.7	2.7
Moderate (−2)	—	—	1.1	1.6	0.5	0.5	1.1	0.5	1.1	1.1
Marked (−3)	—	—	—	—	0.5	0.5	0.5	1.1	0.5	0.5
Death	—	1.6	1.6	1.6	1.6	1.6	1.6	1.6	2.7	2.7

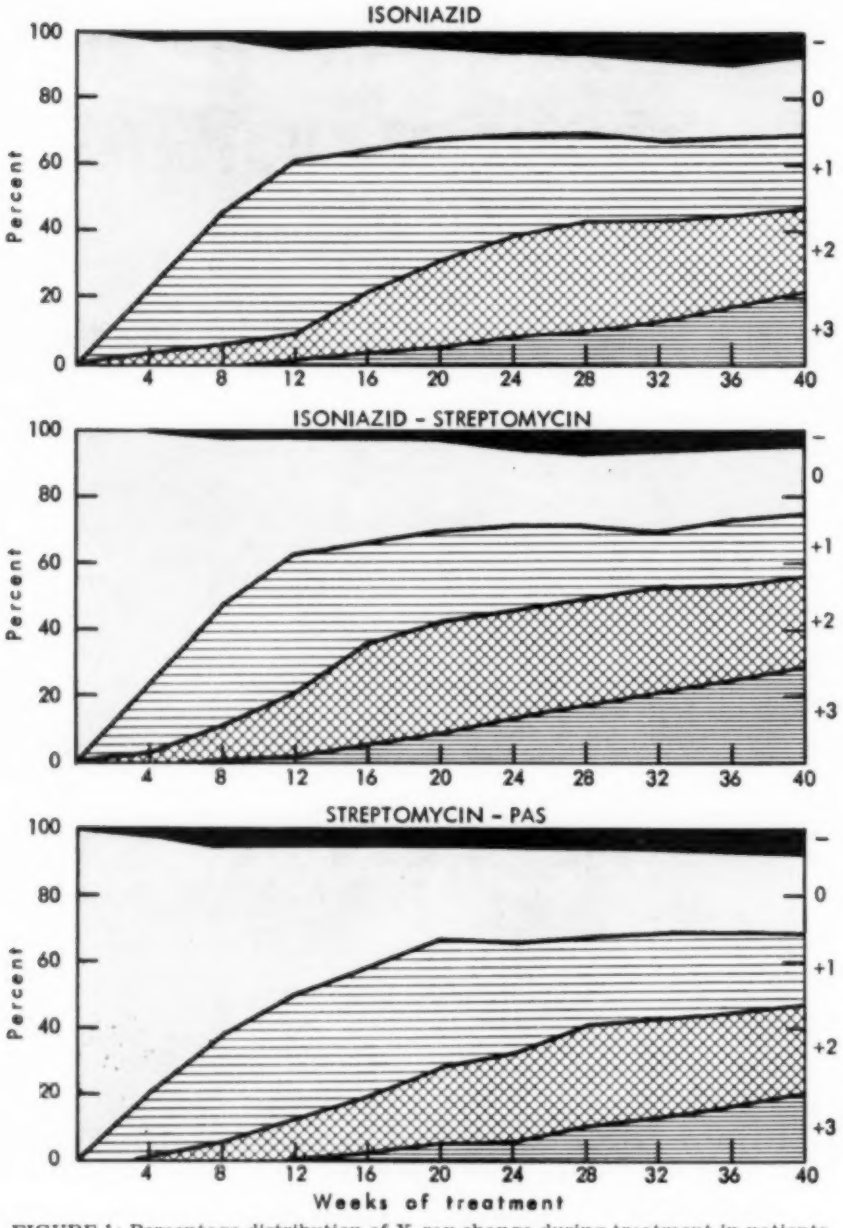

FIGURE 1: Percentage distribution of X-ray change during treatment in patients on three drug regimens, isoniazid, isoniazid plus streptomycin, and streptomycin plus PAS.

and three characteristics of his disease: its stage, duration, and extent. The subgroups were then compared with respect to the proportion of each showing significant x-ray film improvement during treatment.

Age:

The patients have been divided into five age groups as shown in the first section of Table III, the youngest group 14 to 24 years and the oldest group over 55 years. At each of the 10 points of observation, as shown in the first illustration in Figure 3, the proportion of patients showing significant x-ray film improvement decreased with increasing age. From a high of 70 per cent at 40 weeks among those 14 to 24 years old, there was a steady drop in the proportion showing improvement in each older age group to a low of only 30 per cent among those over 55 years old.

Age and race:

A crude adjustment for age has been made by subdividing each racial group into those under and over 45 years of age, as shown in the second section of Table III. The table and the second illustration in Figure 3 show, at four week intervals, the proportion of each group in which significant x-ray film improvement occurred. Throughout treatment, among both whites and non-whites more patients under 45 years of age showed improvement. In those under 45 years old, the proportion who improved was greater among whites than non-whites, while in those over 45 years old, more non-whites than whites showed x-ray film improvement.

After 40 weeks, significant x-ray film improvement was shown in 62 per cent of the white and 53 per cent of the non-white group under 45 years, and 33 per cent of the whites and 48 per cent of the non-whites older than 45.

Age and sex:

The sexes have been similarly subdivided into two age groups, over and under 45 years, as shown in the third section of Table III. A substantially higher proportion of both males and females younger than 45 years im-

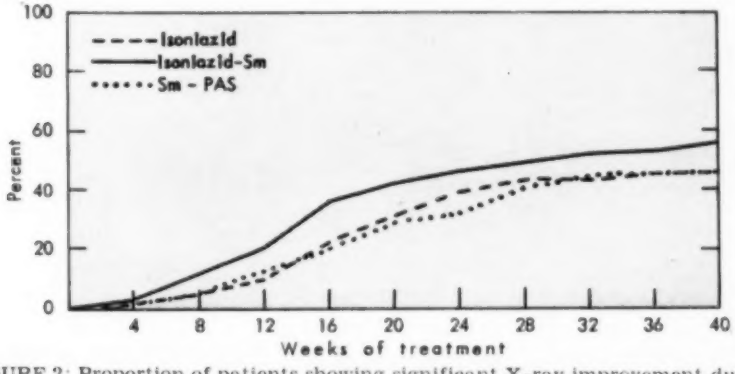

FIGURE 2: Proportion of patients showing significant X-ray improvement during treatment with isoniazid, isoniazid plus streptomycin, and streptomycin plus PAS.

TABLE III: Proportion of Patients Showing Significant X-ray Film Improvement During Treatment When Classified by Age, Race, and Sex.

	No. of Patients	WEEKS OF TREATMENT: 4	8	12	16	20	24	28	32	36	40
Age in Years											
14-24	94	4.3	16.0	27.7	43.6	56.4	60.6	68.1	68.1	68.1	70.2
25-34	127	2.7	7.9	17.3	35.4	48.8	54.3	58.3	57.5	57.5	59.1
35-44	124	2.4	5.6	12.1	25.0	31.5	36.3	39.5	44.4	46.0	47.6
45-54	108	—	3.7	8.3	14.8	20.4	27.8	34.3	37.0	39.8	43.5
55 and over	130	0.8	3.8	6.9	13.8	16.2	20.0	26.2	30.0	30.8	30.0
Age and Race											
Under 45:											
White	184	2.7	9.2	22.3	37.5	49.5	56.5	59.2	60.3	61.4	62.0
Non-white	161	3.1	9.3	13.7	29.8	39.1	41.6	48.4	50.3	50.3	53.4
45 and over:											
White	181	0.6	3.3	6.1	12.7	17.1	22.7	29.3	32.0	33.1	32.6
Non-white	57	—	5.3	12.3	19.3	21.1	26.3	31.6	36.8	40.4	47.4
Age and Sex											
Under 45:											
Male	164	2.4	5.5	14.0	29.9	40.2	44.5	48.2	50.0	51.2	51.8
Female	181	3.3	12.7	22.1	37.6	48.6	54.1	59.7	60.8	60.8	63.5
45 and over:											
Male	191	0.5	4.2	7.9	14.1	18.8	24.6	31.9	36.1	37.2	38.2
Female	47	—	2.1	6.4	14.9	14.9	19.1	21.3	21.3	25.5	27.7

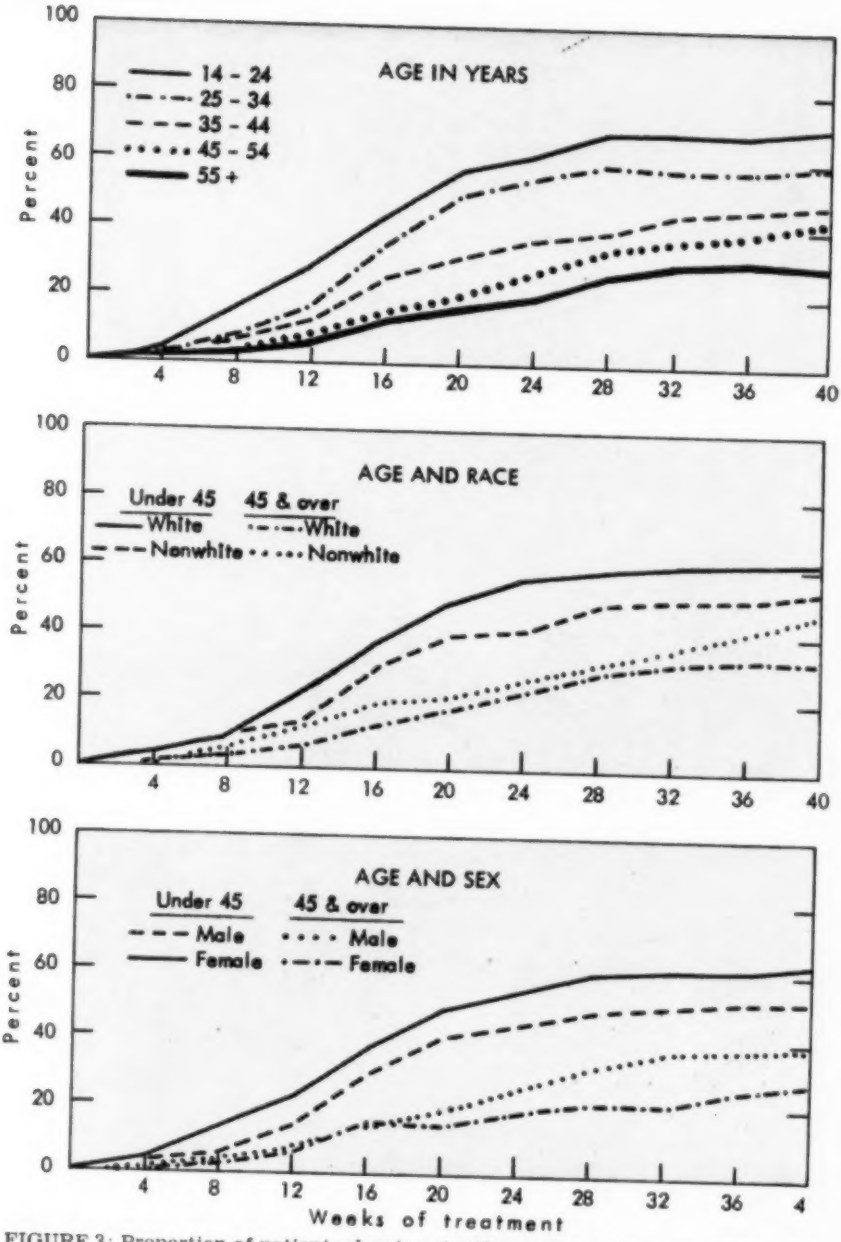

FIGURE 3: Proportion of patients showing significant X-ray improvement during treatment when classified by age, race and sex.

TABLE IV: Proportion of Patients Showing Significant X-ray Film Improvement During Treatment When Classified by Stage, Extent, and Duration of Disease.

	No. of Patients	WEEKS OF TREATMENT: 4	8	12	16	20	24	28	32	36	40
Stage of Disease											
Minimal	37	—	—	13.5	24.3	37.8	40.5	43.2	43.2	45.9	48.6
Moderately advanced	204	2.5	6.9	13.2	24.5	35.8	39.7	46.1	47.1	47.1	50.5
Far advanced	342	1.8	7.9	14.3	26.9	32.2	38.3	43.3	46.5	48.0	48.2
Extent of Involvement											
Unilateral	92	3.3	9.8	19.6	34.8	53.3	55.4	63.0	64.1	60.9	63.0
Bilateral	454	1.8	7.0	12.8	24.2	29.5	35.5	40.5	43.2	44.9	46.0
Duration of Disease											
Under 1 year	248	3.6	9.7	20.6	36.7	49.6	57.3	63.3	66.9	67.3	70.6
1-2 years	133	0.8	6.0	11.3	21.8	25.6	30.1	36.8	40.6	42.9	43.6
2-5 years	100	1.0	5.0	9.0	17.0	20.0	20.0	24.0	24.0	25.0	27.0
Over 5 years	102	—	3.9	5.9	13.7	19.6	24.5	27.5	26.5	27.5	25.5

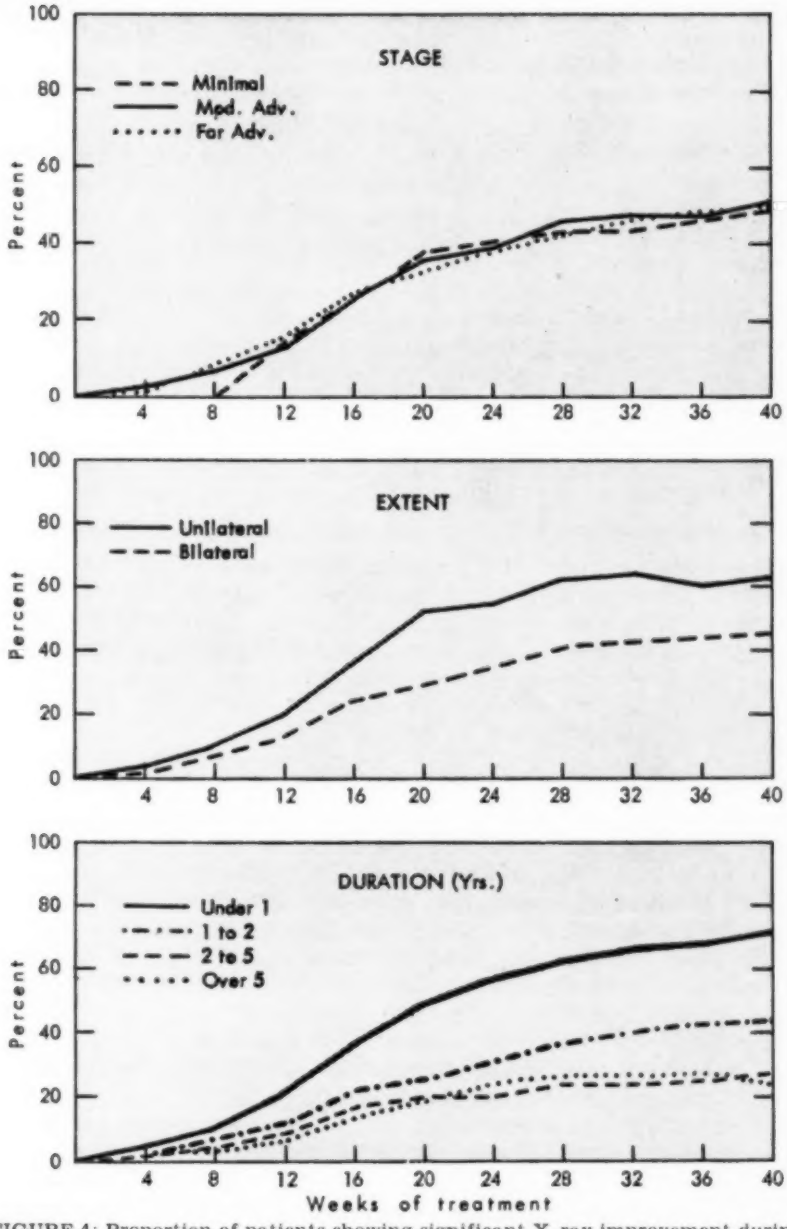

FIGURE 4: Proportion of patients showing significant X-ray improvement during treatment when classified by stage, extent and duration of disease.

proved under treatment than their older counterparts. Among those younger than 45 years, more women than men improved at every point of observation, while among those over 45 years of age, the proportion of patients showing improvement was consistently higher among men.

At the end of 40 weeks, significant x-ray film improvement was reported for 52 per cent of the males and 64 per cent of the females under 45 years of age, and 38 per cent of the males and 28 per cent of the females older than 45 years.

Stage of disease:

Grouped according to the National Tuberculosis Asscciation quantitative classification of extent of disease, the total of 583 patients included 37 with minimal, 204 with moderately advanced, and 342 with far advanced disease. As shown in the first section of Table IV and Figure 4, significant x-ray film improvement appeared in approximately equal proportions of all three groups. At the end of 40 weeks of treatment, the x-ray films of 49 per cent of those with minimal disease, 51 per cent of those with moderately advanced, and 48 per cent of those with far advanced disease had improved to a significant degree.

Extent of involvement:

Those with moderately and far advanced disease have been divided according to extent of involvement into 92 patients with unilateral disease and 454 with bilateral disease. As may be seen in the second sections of Table IV and Figure 4, a higher proportion of the patients with disease in only one lung improved. After 40 weeks of treatment, the x-ray films of 63 per cent of the patients with unilateral disease and 46 per cent of those with bilateral disease showed significant improvement.

Duration of disease:

The length of time since the first hospitalization for tuberculosis has been used as an approximation of the length of time each patient had had tuberculosis. It was recognized that the actual onset of disease invariably preceded hospitalization. However, the difficulties of obtaining exact information on the date tuberculosis first became clinically manifest were so great that the time of hospitalization, a precise date of an observable event, has been used instead. As shown in the third sections of Table IV and Figure 4, significant x-ray film improvement occurred in a markedly higher proportion of patients who had been hospitalized for less than a year. Those first hospitalized between one and two years prior to the study showed the next highest percentage improved. The results of treatment did not differ between the groups first hospitalized two to five years ago and those first hospitalized more than five years before.

At the end of 40 weeks of treatment, the proportion of patients showing significant x-ray film improvement in the groups classified by length of time since first hospitalization ranged from 71 per cent in the less-than-one year group to 26 per cent in the over-five year group.

Discussion

In a cooperative control study of isoniazid, the differences in the results of treatment on three regimens, isoniazid, isoniazid plus streptomycin, and streptomycin plus PAS were slight, but the combination of isoniazid and streptomycin was consistently superior throughout 40 weeks of treatment.

Basically, the motivation for this control study was the continuing search for more effective ways of treating tuberculosis. The results indicate that isoniazid is a chemotherapeutic agent of the order of streptomycin. But the level of that effectiveness deserves attention. In this study, chemotherapy has been combined for each patient with whatever other therapeutic or surgical measures were indicated. The results thus reflect the best that treatment can provide for tuberculous patients today. Yet each of the three regimens, plus all other care, produced significant improvement in only about half of the patients in 40 weeks of treatment. Why did *only* half improve?

In this paper, it has been possible to investigate only a few relationships in a preliminary and exploratory fashion. It is obvious that large numbers of patients must be uniformly studied in order to permit analysis of the effect of a variety of factors, and combinations of factors.

The present limited analysis indicates that in this group of patients the age of the patient, the duration of his disease and whether that disease is unilateral or bilateral were the strongest factors affecting the probability of improvement.

SUMMARY

A control study of isoniazid in 1,500 patients with pulmonary tuberculosis is being carried out by 22 hospitals throughout the country in cooperation with the U. S. Public Health Service. This paper gives preliminary finding on the first 583 streptomycin-sensitive patients who finished 40 weeks of treatment. Comparison of the results in three randomly selected regimen groups shows isoniazid plus streptomycin to be slightly superior to the other two regimens, isoniazid alone and streptomycin plus PAS, which were approximately equal.

The similarity of the results on the three regimens and the fact that only about half of each group showed significant x-ray film improvement during treatment led to an examination of other factors which might influence the response to chemotherapy. The analysis is restricted by two factors, the limited number of items on which comparable information is available for each patient and the number of patients studied.

The frequency of significant x-ray film improvement has been examined in relation to the age, race and sex of the patients and the stage, extent and duration of the disease. Preliminary analysis indicates that in this group of patients the age of the patient, the duration of his disease and whether one or both lungs were involved were the factors most closely associated with x-ray film improvement. The younger the patient and the more recent his disease, the greater the probability that he would improve

during treatment. Disease in only one lung improved more frequently than bilateral disease.

RESUMEN

Se está llevando a cabo un estudio de control en 1,500 enfermos de tuberculosis pulmonar, usando la isoniacida, en 22 hospitales en todo el País. Este estudio se ha emprendido en cooperación con el Servicio de Salubridad Pública de los Estados Unidos de Norteamérica. Este trabajo da cuenta preliminarmente de los resultados obtenidos en los primeros 583 enfermos estreptomicinosensitivos que terminaron 40 semanas de tratamiento. La comparación de los resultados en tres grupos escogidos al azar, muestra que la estreptomicina agregada a la isoniacida, es ligeramente superior a los otros dos regimenes de isoniacida sola y estreptomicina asociada al PAS, estos dos, dando resultados aproximadamente iguales.

La similaridad de los resultados de los tres regímenes y el hecho de que aproximadamente solo la mitad de cada grupo mostraron mejoría radiológica significante durante el tratamiento, condujo al examen de los otros factores que podrían influir en la respuesta a la quimioterapia. El análisis está restringido por dos factores: el limitado número de casos en que se obtuvo información útil para la comparación y el número de enfermos estudiados.

La frecuencia de la mejoría radiológica significante, se ha examinado en relación a la edad, raza y sexo de los enfermos y la estapa, el alcance y la duración de la enfermedad. El análisis preliminar indica que en este grupo, la edad, la duración de la enfermedad y la uni o bilateralidad de la afección, tenían íntima relación con la mejoría obtenida. Mientras más jóvenes son los enfermos, y mas reciente su enfermedad más probabilidades hay de obtener mejoría. Cuando la enfermedad era bilateral, la mejoría era menos frecuente.

RESUME

Une étude de contrôle de l'action de l'Isoniazide chez 1500 malades atteints de tuberculose pulmonaire est en cours dans 22 Hôpitaux du pays, en collaboration avec le Service de Santé National Américain.

Cet article donne les conclusions préliminaires portant sur les premiers 583 malades sensibles à la streptomycine, qui ont poursuivi le traitement pendant 40 semaines.

Les résultats comparatifs de trois groupes parfaitement définis montrent que l'Isoniazide associé à la Streptomycine est très légèrement supérieur aux autres deux modes de traitement: soit l'Isoniazide seul, soit la streptomycine associée au P.A.S. Ces deux derniers traitements ayant la même valeur.

La similitude des résultats des trois modalités de traitement et le fait qu'il n'y eut d'amélioration radiologique vraiment notable que dans la moitié de chaque groupe, nécessitent que soient pris en considération les autres facteurs qui peuvent influencer l'action de la chimiothérapie. Cette analyse se trouve limitée par l'existence de deux facteurs: d'une part, le

nombre peu élevé d'éléments tout è fait comparables chez chaque malade et, d'autre part, la quantité totale des malades à examiner.

La fréquence d'améliorations radiologiques a été étudiée en fonction de l'âge, de la race, du sexe des malades et du temps depuis lequel existe la maladie. Dans les premiers résultats provenant de cette étude, les facteurs qui semblent avoir été les plus intimement responsables des améliorations radiologiques sont: l'âge du malade, la durée depuis laquelle existe la maladie et le fait que la localisation atteint un seul ou les deux poumons. Plus le malade est jeune et plus l'apparition de la maladie est récente, plus il y à de chances qu'il s'améliore au cours du traitement. L'atteinte d'un seul poumon s'améliore plus fréquemment que lorsque l'atteinte est bilatérale.

The Use of Pulmonary Function Tests for Disability Appraisal: Including Evaluation Standards in Chronic Pulmonary Disease*

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The basic data for this paper have been obtained during the past five years from detailed physiological studies on over 500 hard and soft coal miners with pulmonary complaints and a history of many years exposure inside the mines. Data from such a large number of cases, homogenous with respect to the etiology of the fibrosis and emphysema, permit a significantly detailed study of the range of the individual measurements encountered. The test measurements employed should provide as wide a range of values as possible between the normal and the abnormal states which may be encountered in chronic pulmonary disease. One object in studying such a large number of physiological test measurements has been to analyze the significance of the information provided by each, their limitations, and to compare their usefulness.

Vital capacity was measured from rapid spirogram recordings (Figures 1 and 2) of a deep breath followed by blowing the air out of the lungs as rapidly and as completely as possible, and also by reversing the above procedure that is first blowing the air out as completely as possible followed by the deepest possible breath. In normal subjects vital capacity measurements are essentially the same by the two methods, but in chronic pulmonary disease one procedure may give a higher value than the other, hence both methods were employed and the highest value obtained used. The largest volume of air which could be blown out during the first three seconds in the standing position following the deepest possible inspiration was designated the three second vital capacity, normally 95 per cent or more of the predicted vital capacity. The three second vital capacity volume is the maximal effective portion of the vital capacity measurements which can be used with a respiratory rate of 15 or more per minute (a rate of 15 per minute allows four seconds per breath). The volume of air blown out after three seconds is of no functional value, hence the total volume of the vital capacity measurement is of little value as a single measurement when the time factor is not considered. In this laboratory during the past five years, spirograms of vital capacity were taken on a

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fast moving drum which spreads out the tracing so the shape of the curve may be observed and measured. The three second vital capacity measurement, a quantitative expression, conveys most of the information obtained by observing the shape of the first portion of the expiratory spirogram tracing. Gaensler[1] has emphasized in his writings the value of timed capacity measurements. Spirogram tracings reveal the inadequacy of vital capacity measurements obtained on any type of device which gives only a volume measurement without respect to time (Figure 2). Vital capacity

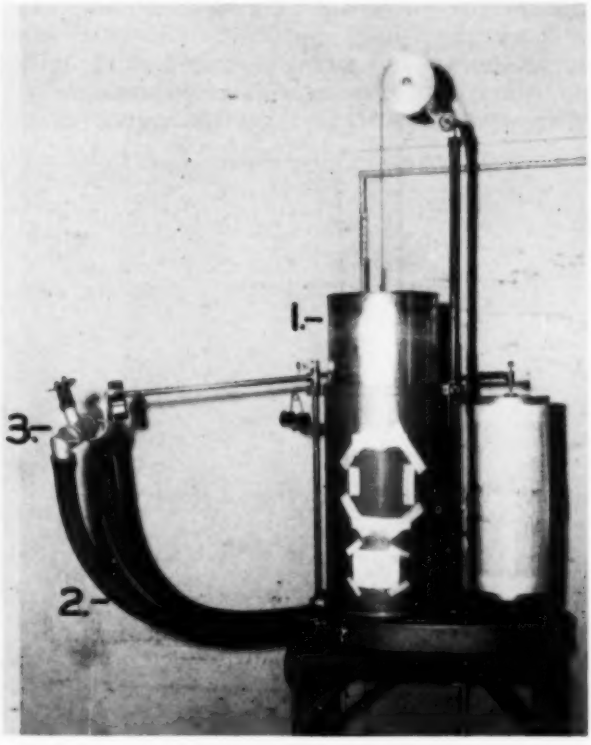

FIGURE 1: The 13½ liter Benedict-Roth type metabolism apparatus (Respirometer, made by Warren E. Collins, Inc., Boston, Mass.) designed with a minimal breathing resistance for voluntary, rapid, deep breathing as used for the maximal breathing capacity measurement (MBC). (1) The large bell (22.9 cms. diameter), (2) the large stiff rubber tubing (2.9 cms. diameter) and (3) the high velocity, low resistance directional valve are the major factors in design responsible for decreasing breathing resistance. Two ink writing pens record permanent kymograph tracings of the measurements, one rate and dept of breathing and the other, an adding pen (Reichert Type), recording the total volume of air for the maximal breathing capacity measurement. Vital capacity measurements both in the supine and standing position were recorded with the kymograph drum rotating rapidly (32 mm. in 12 seconds, the distance between the vertical lines of the kymograph paper). The inside valves and the soda lime cannister were removed and the bell was filled with room air for the vital capacity and maximal breathing capacity measurements. All maximal breathing capacity measurements were obtained with the patient in the standing position with a mouthpiece and nose clip.

as obtained by blowing in a spirometer can be misleading and liable to false interpretation (Figure 2).

Maximal breathing capacity as liters per minute was obtained from the recording of tracings on special apparatus (Figure 1) during voluntary maximal deep and rapid breathing. Each maximal breathing capacity test measurement was of 12 seconds duration followed by a rest interval as long as needed. Several maximal breathing capacity tracings were taken on each case with the rate and depth of breathing varied on successive runs, and the maximal value obtained used as the maximal breathing capacity measurement. The rate and depth of breathing were sought for each subject tested which would provide the highest value. The formula for predicting the maximal breathing capacity both for men and women has been determined from measurements on 55 men and 49 women, not hospital patients and with normal spirogram tracings of vital capacity.

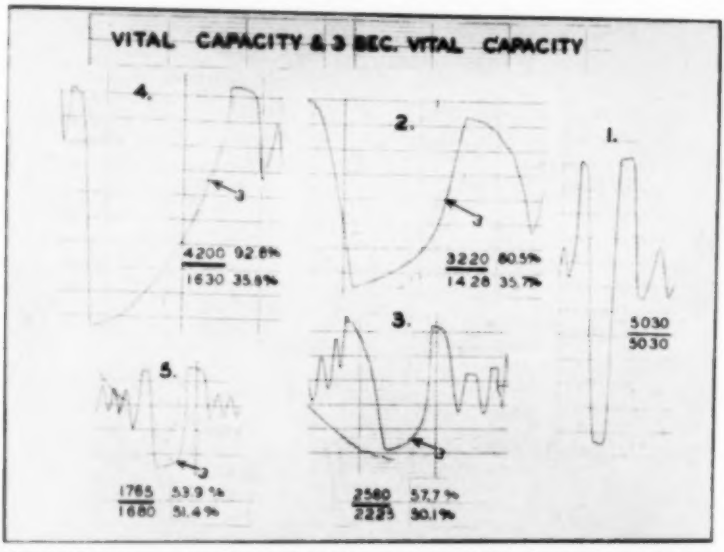

FIGURE 2: Spirogram tracings of vital capacity (VC.) measurements from five subjects in the standing position illustrating a maximal deep breath followed by blowing the air out of the lungs as rapidly and as completely as possible. In the first subject, a normal, (1) the entire volume of 5,030 cc. (normal predicted value) was blown out in less than three seconds (normal three second VC.). In the second subject 2) the total vital capacity was 3,220 cc. of which 1,428 cc. (35.7 per cent of predicted) was blown out during the first three seconds (3 sec. VC.). In the third subject (3) the total vital capacity was 2,560 cc. of which 2,225 cc. (50.1 per cent of predicted) was the three second VC. In the fourth subject (4) the total vital capacity was 4,200 cc. of which only 1,630 cc. (35.8 per cent of predicted) was the three second VC. In the fifth subject (5) the total vital capacity was 1,765 cc. of which 1,680 cc. (51.4 per cent of predicted) was the three second VC. It can be noted in the four abnormal spirogram tracings that the fifth case had the highest per cent for the three second VC. (51.4 per cent) of the normal predicted although the total volume measurement of vital capacity was the lowest (1,765 cc.). Note also that the fifth case had a higher three second VC. with a total vital capacity of 1,765 cc. than the fourth case with a total vital capacity of 4,200 cc. In both the second and fourth cases the blowout during exhalation is abnormally prolonged indicating emphysema.

The predicted maximal breathing capacity in liters per minute for men equal (97 − Age/2) × M^2, BSA, and women equal (83 − Age/2) × M^2, BSA, with standard deviations of 13 and 15 per cent respectively. The presence of bronchospasm was evaluated routinely by measuring the maximal breathing capacity before and immediately after one intermittent positive pressure breathing treatment[2] with the simultaneous administration of a potent bronchodilator drug such as Vaponefrin or Isuprel. The increase in maximal breathing capacity following the bronchodilator treatment was interpreted as representing the amount of bronchospasm present. The average increase in maximal breathing capacity after one intermittent positive pressure breathing treatment with bronchodilator drugs (Isuprel and Vaponefrin) was measured on 400 cases of coal miners silicosis, classified according to the degree of pulmonary function based on comprehensive pulmonary function studies.[3,4] The highest percentage increase (36.5) in maximal breathing capacity was obtained in the far advanced group and the lowest (7.0) in the group with a slight degree. The increase in maximal breathing capacity observed with bronchodilators was no higher with the intermittent positive pressure breathing method of administration than by other meth-

FIGURE 3: An improved set-up of apparatus for determining residual volume by the oxygen open circuit method[5] (Residual Valve Assembly may be obtained from Hayler S. Osborn, Havertown, Penna.). (1) A demand valve is used which supplies oxygen only during the inspiratory phase of breathing. (2) Two small aluminum two-way valves (with a dead space of 65 cc.) are joined by a directional connector valve, which permits switching quickly from the air breathing circuit to the oxygen breathing circuit. (3) A small sensitive indicator guage connected to the air breathing circuit side so that the phase of the respiratory cycle and depth of breathing can be observed and the switch from air breathing to oxygen breathing made exactly at the beginning of inspiration (the inspiratory valve of the air breathing circuit is closed during the expiratory phase of the breath just before the circuit switch). The demand valve and the Tissot gasometer (4) are connected to the two-way valve of the oxygen circuit. The small needle valve (5) shown on the demand valve regulator assembly permits washing out the oxygen breathing circuit with oxygen. (6) Alveolar sampling tube.

ods in the slight group, but in the far advanced groups the increase averaged less than 10 per cent by other methods. A potent bronchodilator drug (such as Vaponefrin or Isuprel) has been routinely administered by the intermittent positive pressure breathing method for 15 to 20 minutes, with maximal breathing capacity tests before and after to determine the degree of bronchospasm present.

The presence and extent of pulmonary emphysema was accurately determined by measuring the residual air volume using an improved apparatus (Figure 3) for the oxygen open circuit method.[5] The residual volume was checked routinely on two runs to within 100 cc., if not the run was repeated. The residual air volume was expressed as a per cent of total lung volume (residual + vital capacity). The air remaining in the lung after a forced expiration is termed residual volume and is normally about 25 per cent of total lung volume. Actually three measurements are involved in the residual volume determination which have an important bearing on the pulmonary function status: (1) the alveolar nitrogen per cent after seven minutes of oxygen breathing, (2) the absolute residual volume with respect to the predicted residual volume for the individual subject and, (3) the residual per cent of total lung volume. Residual volume measurements were not

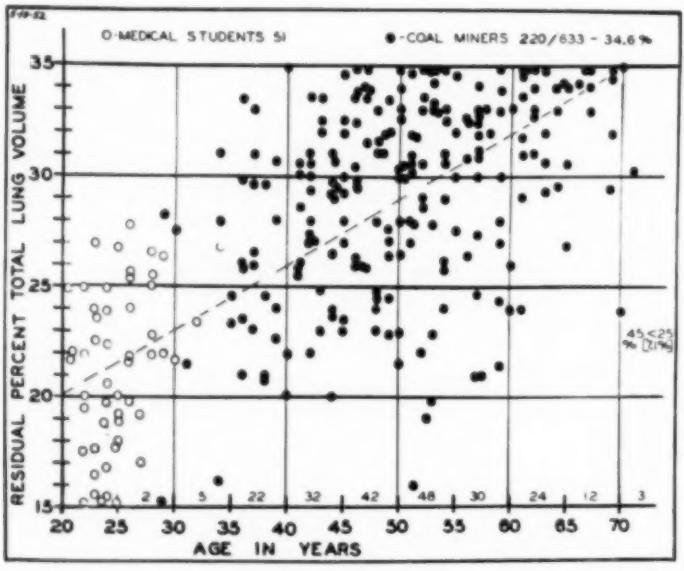

FIGURE 4: The residual volume as per cent of total lung volume, was correlated with the age in years in 220 hard and soft coal miners and 51 men medical students. The average residual volume as per cent of total lung volume for the medical students was 21 per cent. All of the 220 coal miners shown above had residual volumes less than 35 per cent of total lung volume, and these were found in a group of 663 unselected cases of coal miners with pulmonary complaints admitted to the hospital for pulmonary function studies. It should be noted that 45 of the above coal miners had residual volumes less than 25 per cent of total lung volume and one of these was 70 years of age. Observe the dotted line representing the average for the various age groups.

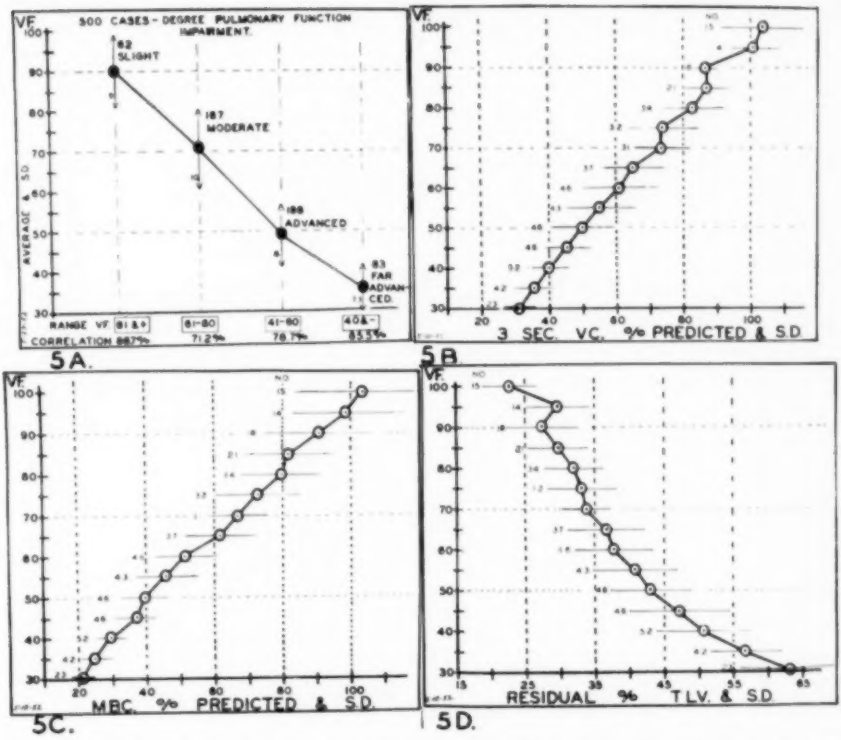

FIGURE 5: Correlation of the ventilation factor (VF.) as per cent on the ordinate with; the degree of pulmonary function impairment (A), the three second vital capacity (B), the maximal breathing capacity (C) and the residual per cent of total lung volume (D).

(A) The ventilation factor is correlated with the degree of pulmonary function impairment in the 500 coal miners classified in four groups based on all the comprehensive tests[3,4] as follows: slight 62, moderate 167, advanced 188, and far advanced 83 cases. The average ventilation factor as per cent (solid black circle) and the standard deviation as per cent (vertical line above and below the black circle) are shown for each of the four groups. The accuracy of correlation of the degree of impairment for the four ranges of the ventilation factor is given at the bottom (i.e. 88.7 per cent of slight group had a factor above 81 per cent).

(B) Correlation of the three second vital capacity as per cent of the predicted vital capacity on the abscissae with the ventilation factor. The 500 cases were divided into 15 groups based on the ventilation factor per cent with step decreases of 5 per cent from 100 to 30 (for example, 31 cases were listed with a ventilation factor of 70 which includes all cases with a range from 67.51 to 72.5). The horizontal line drawn through the average for each of the 15 groups represents the standard deviation for the three second vital capacity as per cent of predicted, and the number of cases in each group is shown by the figure to the left of the line.

(C) The maximal breathing capacity (MBC) as per cent of the predicted (based on formula given in this paper) and the standard deviation as per cent of the predicted maximal breathing capacity in each of the 15 groups was correlated with the ventilation factor as described for Figure 5B.

(D) Correlation of the average residual volume as per cent of total lung volume and the standard deviation of the residual volume as per cent of total lung volume for each of the 15 groups with the ventilation factor as described for Figure 5B.

TABLE I

CORRELATION OF VENTILATION AND BLOOD GAS MEASUREMENTS AND THE DEGREE OF PULMONARY FUNCTION IMPAIRMENT

Degree of Pulmonary Function Impairment Based on All Tests and Number of Cases	Three Second Vital Capacity, Per cent of Predicted	Maximal Breathing Capacity, Per cent of Predicted	Residual, Per cent of Total Lung Volume	Ventilation Factor, Per cent	Arterial Blood Oxygen Saturation Per cent		Oxygen Uptake Step-Up Exercise, cc./min./M2/BSA	Alveolar N_2 After Breathing Oxygen Seven Minutes	Dyspnea Time Step-Up Exercise, Seconds
					Rest	Exercise			
Slight: 62									
Average	90.5	92.0	28.3	90.0	94.9	95.3	546	1.50	95
Standard Deviation	(16.1)	(17.3)	(5.4)	(9.2)	(2.1)	(1.8)	(85)	(0.61)	(29)
Moderate: 167									
Average	72.3	66.1	34.2	71.0	93.2	93.6	507	2.19	119
Standard Deviation	(13.7)	(16.3)	(5.4)	(10.0)	(2.1)	(2.3)	(75)	(0.94)	(46)
Advanced: 188									
Average	50.7	40.6	44.8	49.0	92.0	89.9	450	3.39	144
Standard Deviation	(12.1)	(11.8)	(8.0)	(8.0)	(2.6)	(4.2)	(77)	(1.72)	(44)
Far Advanced: 83									
Average	35.9	26.4	54.8	36.5	90.5	85.5	355	4.27	181
Standard Deviation	(7.7)	(11.3)	(9.0)	(7.3)	(4.6)	(6.7)	(57)	(2.53)	(83)

obtained during periods of upper respiratory infections or asthmatic attacks or other temporary abnormalities which were clinically apparent, so that the residual volume measurements represent the best baseline measurement obtainable on each case. Residual volumes over 35 per cent of total lung volume are abnormal and indicate the presence of pulmonary emphysema.[6,7] A considerable increase in residual volume with minimal disability may be present when compensatory hyperventilation is good and the dyspnea level is not reached even with moderate exercise. A certain per cent of the aged population do have increased residual volumes, greater than 35 per cent of total lung volume, without having subjective symptoms of dyspnea in their daily work. It is felt that this increase is abnormal and does represent emphysema for many individuals even with long exposure to environmental dust hazards and with pulmonary complaints and roentgenologic evidence of silicosis do not have residual volumes above 35 per cent even in the 60 to 70 year age range.

In a large group of coal miners (663 unselected cases) with pulmonary complaints, 34.6 per cent (or 220 cases) had residual volumes less than 35 per cent of total lung volume in age range from 35 to 70 years and with a

TABLE II: EVALUATION STANDARDS

Degree Pulmonary Function Impairment	Normal	Slight	Moderate	Advanced	Far Advanced
Maximal Breathing Capacity*	90 & +	80-90	55-80	35-55	35 & –
Three Second Vital Capacity Standing*	95 & +	80-95	60-80	40-60	40 & –
Residual Per cent of Total Lung Volume	25 & –	25-35	35-45	45-55	55 & +
Ventilation Factor	100 & +	81-100	61-81	41-61	41 & –
Residual Volume**	10 & –	10-20	20-60	60-100	100 & +
Alveolar Nitrogen on 100 Per cent Oxygen for Seven Minutes	1.5 & –	1.5-2.0	2.0-3.0	3.0-5.0	5.0 & +
Arterial Blood Oxygen Saturation, Per cent					
Rest	96-98	94-96	92-94	88-92	88 & –
Step-Up Exercise	96-98	94-96	92-94	85-92	85 & –
Oxygen Uutake with Step-Up Exercise cc./min./M^2/BSA.	500 & +	450-500	400-450	300-400	300 & –
Per cent Oxygen Removed from Inspired Air, During Step-Up Exercise	5.0-6.0	4.0-5.0	3.0-4.0	2.0-3.0	2.0 & –
Dyspnea Time with Step-Up Exercise, Seconds	90 & –	90-120	120-180	180-300	300 & +

*Per cent of Predicted.

**Per cent Increase from Predicted.

significant number of cases in each five year period. The roentgenologic evidence of silicosis classified by stages[6,7] in this group was as follows: first 14.2 per cent, second 20.4 per cent and third 55.8 per cent. Since even in this large group of coal miners who have pulmonary complaints, a 90 per cent incidence of abnormal roentgenologic findings, a history of long exposure inside the mines (average 30 to 35 years) and an age spread from 35 to 70 years, over one third have residual air volumes less than 35 per cent of total lung volume, it would seem most unlikely that the residual volume should exceed 35 per cent of total lung volume in normal individuals even up to 70 years of age. The residual volume measurements observed on the medical students (average 21 per cent of total lung volume) appear in line with those of the coal miners (Figure 4). Emphysema does not appear to be any more a natural part of the aging process than is hypertension. Many individuals have persistent hypertension without complaints over a period of years while actively working, yet their blood pressure is not considered normal; and the same may be said of emphysema, because individuals may have residual volumes of 45 per cent or more of total lung volume without complaints, but this increased residual volume is abnormal and does represent emphysema in most persons.

The three major mechanical factors influencing pulmonary ventilation which are of great importance in the consideration of pulmonary function impairment are: (1) the three second vital capacity, (2) maximal breathing capacity and (3) the residual volume expressed as per cent of total lung volume. A numerical *ventilation factor* has been derived to evaluate the above three important mechanical aspects of pulmonary aeration. The *ventilation factor* was obtained by adding (A) the three second vital capacity standing as per cent of the predicted vital capacity, (B) the maximal breathing capacity as per cent of the predicted maximal breathing capacity and (C) $\frac{\text{normal residual per cent of total lung volume}}{\text{observed residual per cent of total lung volume}} \times 100$ (if the observed residual volume was less than 20 per cent of total lung volume, then 20 was used as a lower figure would tend to weight this factor too heavily) and (D) dividing the sum of A + B + C by 3. Correlation of the ventilation factor with the three components of the measurement and the degree of pulmonary function impairment is shown in Figure 5. The 500 cases were divided into 15 groups based on the ventilation factor per cent with step decreases of 5 per cent from 100 to 30 (for example, 31 cases are listed with a ventilation factor of 70 which includes all cases with a range from 67.51 to 72.5 per cent, Figure 5A, 5B, 5C and 5D). A wide range of values was observed for the ventilation factor between the normal and abnormal states, and these values were well correlated with the timed vital capacity measurements, the maximal breathing capacity and the degree of pulmonary emphysema (Figure 5). The ventilation factor was correlated with the degree of pulmonary function impairment in the 500 coal miners classified in four groups based on comprehensive pulmonary function tests[4] (Figure 5A).

The average resting arterial blood oxygen saturation was above 90 per

cent in all four groups (Table I). The average step-up exercise arterial blood oxygen saturation was increased above the resting level for the slight and moderate groups, and decreased below the resting values for the advanced and far advanced groups (Table I). The standard deviation for the arterial blood oxygen saturation with step-up exercise was markedly greater in the far advanced group, and considerably greater in the advanced group than in the other two groups (Table I). A resting saturation of 95 per cent may decrease to 85 per cent during step-up exercise indicating the presence of severe function disturbance. On the other hand a resting arterial blood oxygen saturation of 88 per cent has been observed to rise to 95 per cent during step-up exercise indicating less function disturbance than the resting blood saturation implied. The change in the arterial blood oxygen saturation with exercise from the resting level has been found to be unpredictable in the individual case, although in general the exercise blood oxygen saturation decreases as the degree of pulmonary emphysema increases and as the ventilation factor decreases.

The ventilation factor was well correlated with the oxygen uptake during step-up evercise (Table I), although there was no correlation with the resting values. A marked decrease in oxygen uptake with step-up exercise indicates an inability to increase the pulmonary blood flow and a lack of expansibility of the pulmonary bed. The ventilation factor was poorly correlated with the per cent of oxygen removed from the inspired air both during rest and exercise.

Dyspnea time was measured following step-up exercise (Table I, (30 step-ups, in one minute on a stool eight inches high), and the character and nature of the subjects reaction following the exercise was carefully noted. The step-up test was performed in duplicate for checks on oxygen uptake and dyspnea time.

Evaluation standards are given for the physiological tests that appear to be most useful in pulmonary function evaluation (Table II), based on analysis of the data obtained from the 500 coal miners.

SUMMARY

A) An accurate evaluation of the degree of pulmonary function impairment can be made from the following physiological tests: (1) Ventilation measurements from spirogram tracings (total vital capacity, three second vital capacity, maximal breathing capacity and the shape of the exhalation curve following a deep breath), (2) the degree of bronchospasm present, (3) the residual volume and alveolar nitrogen per cent after seven minutes oxygen breathing, (4) the arterial blood oxygen saturation at rest and immediately after step-up exercise, (5) the oxygen uptake during step-up exercise and (6) the character and duration of dyspnea after step-up exercise.

B) A numerical ventilation factor has been derived from the three second vital capacity (a timed measurement), the maximal breathing capacity and the residual per cent of total lung volume. In about 75 per cent of the group of 500 coal miners studied the ventilation factor was correct in predicting

the degree of pulmonary function impairment as compared to an evaluation based on comprehensive studies including arterial blood and respiratory gas analysis.

C) Improved techniques and apparatus for measuring maximal breathing capacity and residual air volumes by the oxygen open circuit method are presented.

D) The step-up exercise test is quite satisfactory for obtaining the exercise measurements in pulmonary function evaluation, equal to or superior to the treadmill.

E) Vital capacity as a volume measurement should not be used as a single test of lung function in chronic pulmonary disease, as it can be misleading and responsible for false interpretations.

F) Evaluation standards for the normal and four grades of pulmonary function impairment are given for the physiological tests which appear to be most useful in pulmonary function appraisal.

RESUMEN

A) Se puede valuar el grado de incapacidad funcional pulmonar de acuerdo con las siguientes pruebas fisiológicas: (1) Medidas de la ventilación según los trazos espirométricos (capacidad vital, capacidad vital de tres segundos, capacidad vital máxima y la forma de la curva de exhalación después de la inspiración profunda), (2) el grado de broncoespasmo presente, (3) el volumen residual y el nitrógeno alveolar por ciento después de siete minutos de inhalación de oxigeno, (4) la saturación sanguinea del oxigeno en reposo e inmediatamente después del ejercicio de subida de peldaños, (5) el consumo de oxigeno durante el ejercicio de ascenso de escalera y (6) el caracter y la duración de la disnea después del mismo ejercicio de ascenso.

B) Se ha derivado de la estimación de la capacidad vital en tres segundos un factor numérico de la ventilación (una medida cronizada), así como de la capacidad maxima respiratoria y el porcentaje residual del volumen pulmonar total. Aproximadamente en 75 por ciento de los 500 mineros de carbón estudiados el factor de la ventilación fué correcto al predecir el grado de daño funcional pulmonar, en comparación con la estimación basada en estudios mas completos incluyendo estudio de los gases en la sangre arterial y en los gases respirados.

C) Se presentan técnicas y aparatos mejorados para medir la capacidad máxima y el volumen de aire residual por el método del oxigono en circuito abierto.

D) El ejercicio de escalones es muy satisfactorio para obtener las medidas para valuar la función pulmonar y es igual o superior al sistema del molino movido por los pies.

E) La capacidad vital como medida de volumen no se debe usar como una prueba única de la función pulmonar pues es capaz de llevar a falsas interpretaciones.

F) Se dan los estándares de valuación de la función normal y de cuatro grados de daño funcional pulmonar para las pruebas fisiológicas que parecen ser mas útiles en la estimación de la función pulmonar.

RESUME

A) Une évaluation précise des troubles de la fonction pulmonaire peut être réalisée grâce aux tests physiologiques suivants: (1) mesure de la ventilation par les tracés du spirogramme (capacité vitale totale, capacité vitale-trois secondes, capacité respiratoire maximum, ainsi que la forme de la courbe expiratoire suivant une inspiration profonde), (2) le degré du bronchospasme, (3) le volume résiduel de l'azote alvéolaire pour cent, après sept minutes de respiration dans l'oxygène, (4) la saturation oxygénée du sang artériel au repos, et immédiatement après exercice de montée de marches, (5) la consommation en oxygène au cours de l'exercice de montée de marches, le caractère et la durée de la dyspnée.

B) L'auteur fait dériver le facteur numérique de ventilation de la capacité vitale-trois secondes, de la capacité respiratoire maximum, et de l'air résiduel pour cent du volume pulmonaire total. Dans 75% environ du groupe de 500 mineurs de charbon, qui ont été étudiés, le facteur de ventilation correspondait au degré du trouble de la fonction pulmonaire quand on le comparait aux résultats obtenus par des études complètes, comportant l'analyse du sang artériel et des gaz respiratoires.

C) L'auteur présente des techniques et des appareils qui permettent d'une façon valable la mesure de la capacité respiratoire maximum et du volume de l'air résiduel par un circuit ouvert en oxygène.

D) Le test de la montée de marches est satisfaisant pour obtenir les mesures d'exercice lors de l'évaluation de la fonction pulmonaire.

E) La capacité vitale ne peut être utilisée isolément et comme test de la fonction pulmonaire dans les affections pulmonaires chroniques. Elle peut être à l'origine d'interprétations erronées.

F) Les standards d'évaluation pour la fonction pulmonaire normale et pour les quatre degrés de troubles de cette fonction sont présentés comme tests physiologiques. Ces derniers semblent plus utiles quand il s'agit d'évaluer l'augmentation de la fonction pulmonaire.

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Some Problems of Bronchospirometry
Analysis of 1,000 Procedures*

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Introduction

Clinical assessment of the functional performance of each lung became a subject of interest when asymmetrical distribution of pulmonary disease was first seen roentgenographically. Hopefully, it was thought for some time that the appearance of chest roentgenograms might permit functional comparison. Unfortunately, this static, two-dimensional picture, obtained during full inspiration, frequently led to an erroneous impression of the functional participation of the two lungs.[1,2] Certain refinements of the roentgenographic technique have proved helpful in estimating at least the ventilatory component of pulmonary function. These methods, which introduce a dynamic element in the examination, include direct or photoelectric comparison of two chest plates exposed on maximal inspiration and expiration,[3] fluoroscopic examination of the chest[4] and recording of maximal diaphragmatic and thoracic excursions on one film by means of two exposures through a moving lead grid.[5,6]

Individual ventilation of one lung has been recorded by intubation of its main bronchus[7] or by occlusion of the opposite bronchus.[8] Individual circulation, and by implication, oxygen uptake, has been estimated by angiocardiography[9] or by unilateral pulmonary arterial occlusion with a cardiac catheter fitted with a balloon.[10]

Bronchospirometry, the simultaneous and separate measurement of ventilation and respiration of the two lungs became possible in man with the introduction of the double lumen bronchoscope.[11,12] This procedure is recognized as the only adequate method for determination of differential lung function and serves as a standard by which other differential techniques are evaluated.

Bronchospirometry has seen two stages of development. The introduction of the double bronchoscope led to amassment of considerable valuable data but use of the instrument remained confined to a few research laboratories. It was not generally accepted because it was unwieldy for the doctor, uncomfortable for the patient and there was no wide demand for clinical differential functional analysis in the then infant field of thoracic surgery.

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The development of pliable double-lumen catheters for bronchospirometry[13,14] coincided with rapid advances in thoracic surgery and more radical treatment of pulmonary tuberculosis. The subsequent introduction of bronchospirometry to medical centers and sanatoria throughout the world has emphasized certain problems and difficulties associated with the procedure which will be the topics of this presentation. At present the demand for bronchospirometric examinations greatly overtaxes available facilities. It is hoped that a discussion of its various problems will stimulate interest in the procedure and hence make it more generally available.

Bronchospirometry as an Adjunct to Pulmonary Function Studies

Bronchospirometric examination should not be performed without concomitant investigation of overall function. A number of reports have appeared which deal solely with bronchospirometric findings in certain diseases or after various operations. We are also frequently asked to study patients with this procedure alone. Because it is as difficult to gain a clinical impression of overall ventilatory insufficiency as it is to estimate the functional participation of each lung, total pulmonary functional studies should always preceed bronchospirometry. Often these initial studies, by the information they give, eliminate the need for bronchospirometry. Ill patients may thus be spared intubation when an inadequate total function precludes collapse or resection therapy. This does not apply if severe pulmonary insufficiency is thought to be largely due to total loss of function of one lung. This situation, if confirmed by bronchospirometry, permits extensive surgery. Other patients may have normal or better than predicted total function. For these, extensive surgery may be planned irrespective of initial functional participation of each lung.

For compilation of data concerning the effect of disease or treatment on pulmonary function it is also necessary to precede bronchospirometry with total pulmonary functional studies.

Basal oxygen uptake cannot be derived by addition of oxygen uptakes of the two lungs during bronchospirometry. Local and general premedication, the unaccustomed procedure and the relatively short time in the recumbent position are responsible for significant changes in cardiac output and oxygen uptake during bronchospirometry.[15] Basal ventilation cannot be obtained for the same reasons. The resistance of the catheter is an additional cause of hyperventilation. Usually there is a marked increase of the respiratory rate and a slight decrease of tidal volume.

Lack of training, resistance breathing and accumulated secretions are responsible for a smaller vital capacity than that obtained by ordinary spirometry. Analysis of 652 split function studies showed that the mean added vital capacity of the two lungs under the best circumstances averaged 88 per cent of the mean actual vital capacity.[16] Even the subdivisions of the vital capacity do not have the same relationship during bronchospirometry because resistance breathing, however slight, causes an elevation of the pulmonary resting position with a decrease of the inspiratory capacity and a relative increase of the expiratory reserve volume.[12,16]

Moderate exercise during bronchospirometry has been made possible by the relatively large internal diameters of newer bronchospirometric catheters.[17] Nevertheless, the work required for a given exercise while breathing through a tube is probably considerably greater than for the same exercise without the tube.[18]

The maximum breathing capacity cannot be measured during bronchospirometry. It is difficult to maintain correct catheter position during the violent breathing effort. More important, the decrease of the internal diameter of the airways is considerable even with catheters of the best design. This greatly impedes the rapid flow of air because the resistance to flow varies inversely as the fifth power of the diameter of the tube.[16] In 30 patients in whom an attempt was made to obtain a maximum breathing capacity during the procedure, ventilation was on the average less than 50 per cent of the maximum breathing capacity determined without the tube, with a high velocity valve and Douglas bag.

From a research standpoint it is therefore necessary to measure resting values, exercise requirements and maximal efforts without the disturbing and obstructing catheter. The data derived from bronchospirometry for each lung are expressed as per cent of the total function and are then applied to actual volumes derived from overall studies. This makes it possible to appreciate the actual ventilatory and respiratory contribution of each lung. Then, if changes in total function occur due to therapy or due to the natural evolution of the disease, the bronchospirometric data indicate whether this overall change was due to an altered functional relationship between the two lungs or due to general functional improvement or deterioration.

Bronchospirometric observations without support of other functional evaluations should be confined to studies where basal and maximal values cannot be obtained, as in the experimental animal. A comparison of split function studies alone also appears justified when rapid alterations of the functional relationship of the two lungs is anticipated as during induction of intrapleural pneumothorax, during changes from the supine to other positions and under anesthesia during thoracic surgical procedures.[19]

Resistance Breathing

Simultaneous analysis of ventilation and gaseous exchange of the two lungs entails artificial separation of the airways by rubber or metal tubes. A consequent reduction of the cross sectional diameter of the airway to each lung is unavoidable. Some qualitative effects of this resistance breathing have been mentioned. It has been suspected that a quantitative difference might exist between the resistance encountered by the two lungs. A number of studies were made to evaluate this effect.[16]

The resistance to flow is easily measured when air is blown through one limb of a bronchospirometric catheter. A water manometer is attached to a side arm at the proximal end of the lumen which records the pressure necessary to produce air flow at a given rate. Since this "pressure drop"

or resistance becomes larger as the rate of air flow increases, it is necessary to measure rate of flow as well.

The resistances offered by various bronchospirometric catheters to a flow rate of 30 liters per minute are shown in Figure 1. Even higher rates of flow are encountered in the adult at rest. The double-lumen catheters proposed by Gebauer,[13] Zavod[14] and Carlens[20] have a larger resistance on the left, partly, because the airway to the left lung is somewhat longer. When the single-lumen catheter of Norris and associates[21] is used the airway to the right lung consists of the natural air passages partially obstructed by the rubber tube leading to the left bronchus. The resistance for the right lung, measured in a specimen of human trachea and larynx, is many times larger than for the left, even when the vocal cords are forcibly separated. The different resistances of the two sides of these catheters increase the work of breathing unequally.

The obstructions offered by these tubes can be brought into proper perspective by comparing them with pressure gradients measured in the normal and abnormal human airways by the flow interruption technique[22,23] (Figure 1). The catheters offer four to 18 times greater resistance than the normal human aiway from mouth to alveoli. The resistances are at best equal to, and at worst, four times greater than those measured in patients with severe bronchial asthma or pulmonary emphysema (Figure 1).

Resistances were measured at flow rates from five to 40 liters per minute. With most tubes the resistance increased more rapidly than the rate of

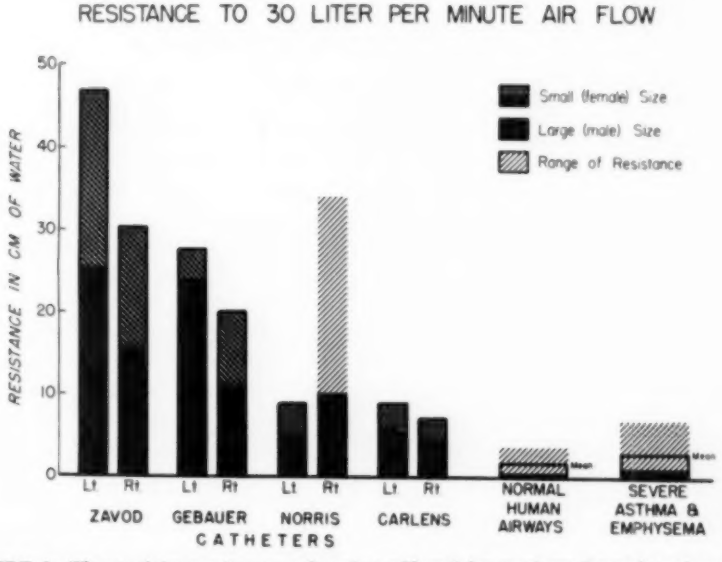

FIGURE 1: The resistance in cm. of water offered by various bronchospirometric catheters and by the normal and abnormal human airways to air flow at the rate of 30 liters per minute. The airway resistance in normal subjects and in patients with severe pulmonary emphysema or bronchial asthma was measured by Otis and Proctor from the mouth to alveoli by the flow interruption technique.[22,23]

flow. This non-linear relationship suggests that the flow is turbulent rather than streamlined, a conclusion supported by theoretical calculations.[16] The non-linearity causes a relatively greater handicap for the major lung which moves air at higher rates. These inequalities are not great during resting ventilation and can be minimized by use of large-diameter tubes of the most recent design.[20] The unequal resistances become a factor of great importance during exercise and invalidate results of differential maximum breathing capacities performed with the catheter in place.

The elevation of the pulmonary resting volume (functional residual capacity) due to the catheter obstruction was evaluated by spirometry. One limb of the tube was interposed as an external resistance. The increase of functional residual capacity for both lungs varied from 200 to 1,900 cc. with the various tubes under investigation. This becomes an important consideration when the inspiratory capacity and expiratory reserve, determined by bronchospirometry, are reported separately. The same effect makes use of tubes with the largest internal diameter mandatory when the functional residual capacity of the two lungs is determined separately.[24]

Effect of the Oxygen Concentration of the Inspired Gas

Another factor which has been thought to affect the two lungs unequally is breathing of an oxygen-enriched atmosphere during recording bronchospirometry. Ideally, spirometry and bronchospirometry should be performed with room air as the inspired gas to reproduce normal resting conditions. Closed-system rebreathing spirometry is generally favored because a visual record of respiratory excursions is obtained. Room air cannot be used because oxygen is constantly removed from the spirometer and after a few breaths an abnormally low oxygen concentration is produced. A number of variations of closed-system spirometry have been described which permit constant room air breathing as well as recording. Most of these methods, which were recently reviewed,[25] do not permit measurement of oxygen uptake and all are too complex for adaptation to bronchospirometry.

The concern over the artificial conditions existing during oxygen bronchospirometry has led to use of an open-circuit technique. Room air is inhaled through one set of valves and the expired air of the two lungs is collected in rubber bags whose volume and gaseous composition is measured later.[27,28] In addition to the advantage of room air breathing this system offers less resistance than spirometers and carbon dioxide output is measured more easily than with closed-circuit methods. The method has not found wide acceptance because it does not permit estimation of differential vital capacities, because it requires multiple gas analysis for evaluation of respiratory gas exchange and because no visual record of respiratory excursions is obtained. Malposition of the catheter and technical difficulties are therefore easily overlooked.

We have adapted a drum-balloon system for bronchospirometry which permits graphic recording as well as room air breathing.[25] Inspiration takes place from balloons filled with room air suspended within air-tight drums. The expired air is directed into the drums around the balloons.

The volume changes occurring in the drums are reflected by the movement of recording spirometers connected to the drums. If the balloons are thin, the volume recorded by the spirometers corresponds exactly to the volumes exchanged by the two lungs, and if the drums are small, artefacts due to temperature changes are minimized.

Bronchospirometry was performed in 18 patients first with room air and immediately afterwards with an oxygen-enriched atmosphere. In normal subjects and in patients with slight or moderate unilateral functional impairment due to carcinoma, tuberculosis or trauma there was no difference in relative oxygen uptake on changing from room air to oxygen breathing. In seven patients with severe unilateral pulmonary insufficiency due to carcinoma, tuberculosis, empyema or pulmonary vascular anomalies the mean oxygen uptake on the affected side was three per cent of the total on room air breathing and 12 per cent of the total on oxygen breathing. The ratio of ventilation and vital capacity remained unchanged.

The greater participation in oxygen uptake by a severely diseased lung on breathing an oxygen-enriched atmosphere was ascribed to three factors:

(1) In portions of the lung where bronchi are involved, distal ventilation may be insufficient to raise the alveolar oxygen tension much above that of the pulmonary arterial blood. On oxygen breathing enough oxygen may diffuse past the obstructing bronchi to raise the alveolar oxygen tension at least to normal levels.

(2) Alveolar membranes are fibrosed, thickened and edematous in many parts of the diseased lung. The diffusion coefficient for oxygen may be so high that a normal alveolar oxygen tension is insufficient for effective oxygenation of the capillary blood. In such normally ventilated parts of the lung oxygen breathing may raise the alveolar oxygen tension many times above normal. The larger gradient between the pulmonary arterial blood and the alveoli may then permit oxygen transfer in spite of damaged membranes.

(3) The previous two mechanisms imply that during room air breathing portions of the diseased lung are perfused with blood without being effectively ventilated. If this occurred in extensive portions of the lungs, the peripheral arterial blood would be unsaturated. This was not true in four of five patients whose arterial blood was examined during room air bronchospirometry, suggesting that local vasoconstriction exists in underventilated portions of the diseased lung. This vasoconstriction may be relieved by inhalation of oxygen thereby increasing the fraction of the right cardiac output flowing through the diseased lung. The absence of arterial hypoxia on breathing room air and the increased oxygen uptake on breathing an oxygen enriched atmosphere can both be explained by this mechanism. The experimental work of others, on which this speculation is based, has been reviewed.[25]

It can be concluded that conventional oxygen bronchospirometry gives an incorrect impression of the functional participation of greatly damaged lungs but does not measurably alter results of the procedure in normal subjects and in patients with only moderate unilateral pulmonary involvement.

Effect of Bronchospirometry on the Subsequent Course of Pulmonary Tuberculosis

The effect of intubation with bronchoscopy and bronchospirometry on the subsequent course of pulmonary tuberculosis has been a subject of concern to both patients and physicians. Although relevant data of the effect of bronchospirometry have not been published, a number of extensive studies have been made of results following bronchoscopy. A review of these reports reveals little variation from clinic to clinic in the number of febrile reactions, the incidence of increased cough and expectoration and the percentage of patients who show evidence of increased activity or new areas of involvement by roentgenograms.[29] There was little agreement, however, as to the relationship of bronchoscopy to this worsening of the disease. Some could not escape the fact that in individual patients symptoms appeared shortly after the procedure and roentgenographic changes occurred in patients who previously had stable disease for long periods of time. Others felt on statistical grounds that, contrary to clinical evidence, bronchoscopy had no effect on the natural evolution of the disease.

Our own observations, following bronchospirometry, are based on roentgenograms obtained the day before the procedure and one week and six weeks after bronchospirometry. Four-hour temperature charts were maintained for one to six weeks after each examination. The observations suggest that (1) an adverse effect on the subsequent course of pulmonary tuberculosis may, in rare instances, be directly attributed to the procedure and (2) bad results, when they do occur, are not due to intubation but rather to excessive preoperative medication, intensive topical anesthesia and inadequate postoperative care.

Our initial experience involved 97 patients with pulmonary tuberculosis who were followed at least one week and usually six weeks after bronchospirometry. All were premedicated with 100 mgm. of a short acting barbiturate the night before operation and the next morning. All received 10 to 16 mgm. morphine sulfate and 0.4 to 0.6 mgm. atropine sulfate subcutaneously one-half hour before the procedure. Forrestier's solution, a long acting topical anesthetic with phenol and cocaine as the active ingredients, was used. Postoperative care included treatment of hoarseness and a painful throat as well as codeine sulfate for cough.

The incidence of febrile reactions and extensions of disease, observed on roentgenograms, is shown in the upper half of Figure 2. Nearly half of all the patients had a temperature elevation of less than 2 degrees F. and over 13 per cent had a high fever. New areas of infiltration and extension of existing involvement were observed in 8.3 per cent. Patients with far advanced disease and severe symptoms were more prone to high fever and adverse roentgenographic changes.

Typical temperature charts of three patients who showed evidence of spread of the disease are shown in Figure 3. The first patient had pulmonary tuberculosis in its most unstable form with frequent preoperative temperature elevations to 99.6 degrees F. The second patient had a severe

febrile reaction following bronchoscopy which was not accompanied by roentgenographic changes. Some months later, following bronchospirometry, a severe fever was followed by new infiltration at the base of a previously minimally involved lung (Figure 4). The last patient (Figure 3) was the only one in this group who had stable and only moderately advanced disease and who had never had a temperature elevation, cough or sputum before bronchospirometry.

The regime of medication and postoperative treatment was then changed. The next 333 patients with active tuberculosis received 100 mgm. of a short-acting barbiturate the same morning to inhibit toxic reactions to the topical anesthetic. No other medication was given and 0.25 per cent tetracaine (8:1 dilution of commercial Pontocaine) was used for topical endotracheal anesthesia. After bronchospirometry no sedatives or anti-tussives were allowed, postural drainage was performed at frequent intervals and 100,000 units of penicillin were given twice a day intramuscularly for three days. The selection of patients for bronchospirometry remained unaltered.[29]

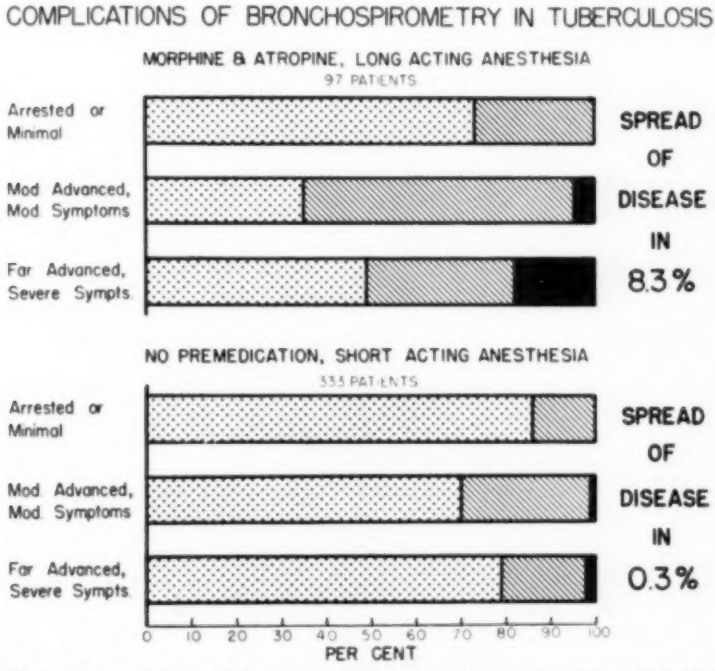
COMPLICATIONS OF BRONCHOSPIROMETRY IN TUBERCULOSIS
MORPHINE & ATROPINE, LONG ACTING ANESTHESIA
97 PATIENTS
Arrested or Minimal
Mod Advanced, Mod Symptoms
Far Advanced, Severe Sympts
SPREAD OF DISEASE IN 8.3%
NO PREMEDICATION, SHORT ACTING ANESTHESIA
333 PATIENTS
Arrested or Minimal
Mod Advanced, Mod Symptoms
Far Advanced, Severe Sympts
SPREAD OF DISEASE IN 0.3%
0 10 20 30 40 50 60 70 80 90 100
PER CENT

FIGURE 2: The incidence of low grade and severe febrile reactions and of spread of the disease following bronchospirometry in patients with varying degrees of pulmonary tuberculosis. The first 97 patients were premedicated with a barbiturate, morphine and atropine. Forrestier's solution was used for topical anesthesia and codeine was given postoperatively for control of cough. The second group of 333 patients received only a barbiturate before examination and 0.25 per cent tetracaine was the topical anesthetic. No anti-tussives were allowed and penicillin and postural drainage therapy was used for three days after the procedure.

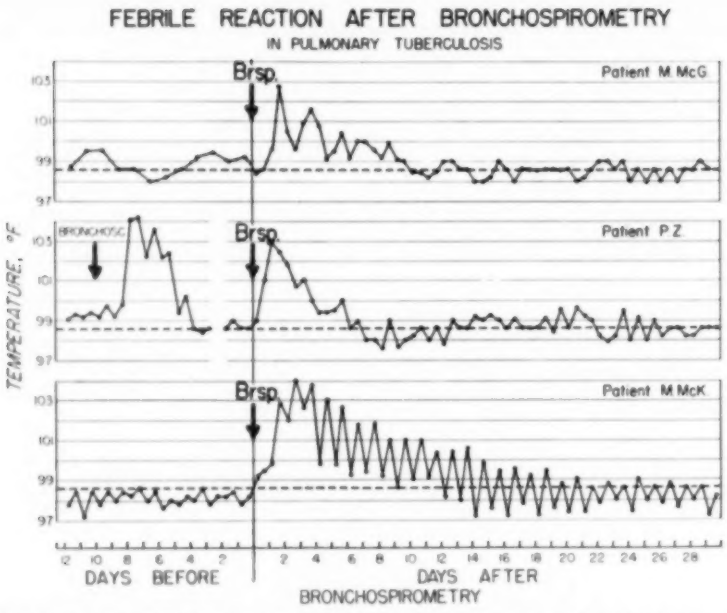

FIGURE 3: Postoperative temperature charts of three patients who showed new foci of pulmonary tuberculosis two to six weeks after bronchospirometry. The first two patients had far advanced unstable disease with frequent low grade fever before examination. The second patient had a febrile course after bronchoscopy some months before. The last patient had stable, only moderately advanced disease and had been afebrile and without cough or expectoration for two years prior to bronchospirometry.

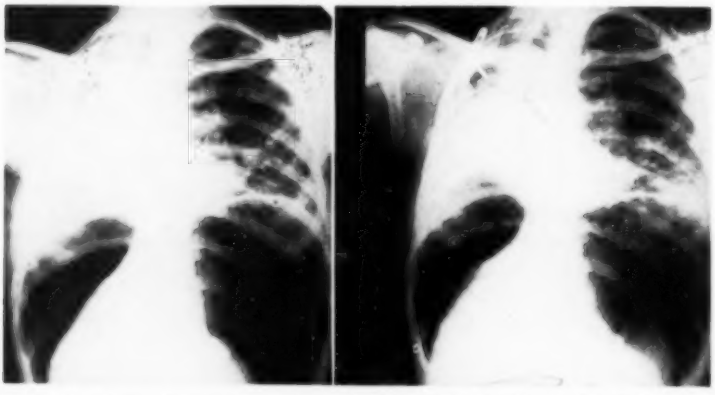

FIGURE 4: Chest roentgenograms of patient P.Z. obtained one day before and one week after bronchospirometry. A new area of infiltration at the costophrenic angle of a previously minimally involved left lung was noted. This shadow persisted for more than six months in spite of streptomycin therapy. This patients temperature chart is shown in the center of Figure 3.

With this new regime the incidence of all febrile reactions was reduced from 49 to 24 per cent, a high fever was noted in two instead of 13 per cent and only one of the 333 patients showed roentgenographic evidence of spread of the disease. The number of adverse results was thus reduced from 8.3 to 0.3 per cent (Figure 2).

We agree with Amberson[30] and Radner[31] that the occasional unfavorable effect of tracheal intubation on the course of pulmonary tuberculosis is not due to the endoscopic procedure itself but rather to retention of purulent material and implantation of bacillus laden secretions in previously unaffected parts of the lung. Preoperative and postoperative medication and topical anesthesia all favor such retention. Barbiturates cause sleep for many hours after the procedure, atropine makes the secretions more viscid and hence more difficult to raise and morphine acts as a potent anti-tussive. Forrestier's solution deprives the patients of endobronchial sensation for one to two hours and codeine, given postoperatively, prolongs the period of sputum retention. Results with a regime which altered as many of these factors as possible confirmed these assumptions.

Contraindications

Ulcerative tracheo-bronchial tuberculosis and recent hemoptysis have been mentioned most frequently as absolute contraindications to bronchospirometry.[29,32] We have adopted these contraindications with the provision that the hemoptysis is not more than two weeks old. A deformed tracheobronchial tree has occasionally made proper positioning of the catheter difficult. When there is severe stricture of the left bronchus due to fibrosis or tumor some information is obtainable by intubating the right main bronchus. The value of the procedure is naturally reduced under the circumstances.

The potential danger of bronchospirometry in tuberculosis has been discussed and its adverse effects on toxic patients with far advanced unstable disease was demonstrated in Figure 2. Following our initial experiences with 97 patients (Figure 2) we planned to avoid bronchospirometry in patients with this type of disease. Unfortunately these were the very patients in whom information concerning differential function was most urgently needed. Retrospective analysis of the extent and severity of tuberculosis in 333 patients examined since then (Figure 2) reveal that 10 per cent were classified as having far advanced disease with severe symptoms. This represented the same proportion that had been encountered among the initial 97 patients.

A number of conditions were studied without difficulties in which bronchospirometry had been previously considered prohibited. In patients with bronchiectasis and copious secretions uneventful intubation was always possible after intensive postural drainage and preoperative antimicrobial therapy. Dyspnea has been mentioned as a contraindication by all investigators except one.[33] We have encountered no special difficulty in the presence of this symptom and have performed the procedure on patients with maximum breathing capacities of 16 and 18 liters per minute.[29] On

the contrary, patients with marked pulmonary insufficiency had less opportunity to alter their pulmonary resting position and could not experiment with different rates and depths of respirations. Their tracings were therefore usually more easily interpreted. Thirty-four per cent of all patients reported some dyspnea during daily exercise prior to the examination and 11 per cent were short of breath on minimal activity.[29]

The Outcome of Bronchospirometry

The results of the first 724 split function studies performed at the Sanatorium Division and the Heart Station are listed in Table I. Satisfactory information concerning differential oxygen uptake, vital capacity and resting ventilation could be obtained from 89 per cent of all procedures. No useful data could be derived from 4 per cent of the examinations.

The catheter could not be introduced into the left main bronchus on seven occasions. This was always due to a deformed tracheo-bronchial tree or strictures involving the trachea or left main bronchus. On three occasions general anesthesia had to be resorted to in children or psychotic patients. Only one patient could not tolerate the catheter because of dyspnea. Technical difficulties with the recording apparatus and defective catheters prevented adequate results five times. An occasional cause of unsatisfactory tracings was occlusion of the lateral opening of the catheter for the right lung by a deviated trachea.[29] This difficulty was eliminated by use of the Carlens catheter[20] which has a distal end opening for the right as well as the left lung. Incorrect positioning of the tube was by far the most frequent cause of unsatisfactory results from a single tracing. When the procedure outlined below was followed it was possible to salvage useful information.

Precautions During Bronchospirometry Assuring Reliable Results

The key to satisfactory bronchospirometry is adequate topical anesthesia. The method we use has been recently outlined in detail.[29] The short duration of action of dilute tetracaine requires rapid progress of the examination. Forrestier's solution is preferred if prolonged special studies are planned.[33] When cough or accumulated secretions make intubation or the

TABLE I

OUTCOME OF BRONCHOSPIROMETRY PERFORMED ON 724 OCCASIONS

	Number	Per cent
Excellent	276	38
Good (base line somewhat variable)	247	34
Fair (base line variable, breathing irregular)	121	17
Total, satisfactory results	644	89
Poor (vital capacity or oxygen uptake or resting ventilation could not be determined)	52	7
No useful data	28	4
Total, unsatisfactory results	80	11

conduct of recording difficult it is best to abandon the procedure and repeat it another day.

The associated apparatus is checked before the patient arrives. Proper functioning of recording equipment should be assured particularly if the instruments are used only occasionally. The resistance characteristics of the catheter should be measured after each sterilization. The rate of flow can be measured roughly by the steel ball gage if an oxygen tank, fitted with a reduction valve, is used to force gas through the tube; the resistance can be recorded with a water manometer of a pneumothorax machine.[16]

Proper positioning of the catheter depends on accurate localization of the carina which is facilitated by a maneuver suggested by Wright.[33] The tip of the tube is observed as it jumps over the carina when the catheter is turned from right to left at the proper level. The tip should be advanced at least 2 cm. into the left main bronchus or the distal balloon may not properly seal the bronchus. It should not be advanced more than 4 cm. or the balloon may occlude the orifice of the left upper lobe bronchus. Fluoroscopic observation or spot film control is also important when the Carlens catheter is used. Its carinal hook is helpful but does not entirely prevent faulty positioning.

Following initial placement we obtain a spot film of the trachea and carina. A bronchospirogram is recorded for four to eight minutes. At the end of this period a second spot film is exposed to assure that the catheter has not moved during recording. The tip is again visualized on the screen. If it appears within the bronchus less than 2 cm. from the carina it is advanced about 1 cm.; if it is more than 4 cm. from the carina it is withdrawn about 1 cm. Another spot film and a second tracing is then obtained. These maneuvers assure that at least one bronchospirogram was recorded with the catheter in the proper position and later comparison of tracings with corresponding catheter position is possible. Results may then be reported with confidence.

Special Procedures

Differential residual volume determination: The magnitude of the residual volume of each lung is of considerable interest in the study of unilateral pulmonary disease and in the analysis of the effect of collapse and resection procedures. The accurate determination of these volumes has been made possible by the room air recording bronchospirometer[25] used in conjunction with the low-resistance selfpositioning Carlens catheter.[20] With this technique it could be shown that thoracoplasty and phrenic interruption reduce the total lung capacity mainly at the expense of the inspiratory capacity while extrapleural pneumothorax reduces chiefly the residual volume.[24] The effect of phrenic interruption and intrapleural pneumothorax was not confined to the involved side. Parenchymal disease caused a moderate reduction of inspiratory capacity as well as of functional residual capacity. Pleural infection or trauma severely reduced the inspiratory capacity while the functional residual capacity remained rel-

atively normal. The volume compartments of the lung remaining after pneumonectomy could be measured before the other lung was removed.

Differential analysis of distributional factors: The percentage of nitrogen remaining in the "alveolar air" of each lung after seven minutes of pure oxygen breathing served as an index of the effectiveness of intrapulmonary mixing.[24] Abnormal distributional factors within one lung could be demonstrated when combined study of both lungs had failed to reveal any abnormality. The most striking unilateral mixing defects were demonstrated in lungs immobilized by a rigid chest wall after thoracoplasty or immobilized by a "cortex" in the presence of empyema or organized hematoma.

Pneumotachography of each lung: Instantaneous flow measurements for each lung were not informative as long as the earlier flexible double-lumen catheters were used for separation of the airways. Resistance breathing patterns due to catheter obstruction masked abnormalities due to bronchopulmonary disease.[16] Later a double pneumotachograph designed according to Silverman and Whittenberger was used in conjunction with the Carlens catheter. Obstruction on one side alone could be demonstrated in patients with carcinoma involving secondary bronchi. Predominantly unilateral obstructive patterns were noted in some patients with bronchial tuberculosis and sarcoidosis. A marked difference of the inspiratory-expiratory time ratio of the two lungs were observed occasionally.

Bronchospirometry during exercise: Differential oxygen uptake and ventilation was recorded during mild exercise in the supine position. The average oxygen uptake was increased 340 per cent over resting values. In most patients the observations of Bjorkman and Carlens[17] were confirmed: oxygen uptake of the two sides increased in proportion to the resting ratio. In two patients with only moderate unilateral functional impairment the diseased lung appeared unable to increase its oxygen uptake although the ventilation ratio remained unchanged. With exercise the resistance to blood apparently increased much more on the diseased side than on the well side. A larger proportion of the cardiac output was therefore shunted through the well lung.

Bronchospirometry during thoracic surgical procedures: Endobronchial inhalation anaesthesia was administered with the Carlens catheter on over 200 occasions. With the aid of a double three-way valve designed by Cincotti and associates[19] it was possible to apply suction, anesthetic gases or spirometry to each lung separately, in sequence or simultaneously. Bronchospirograms were obtained before operation in the supine position, during various phases of the operation in the lateral decubitus position and again supine at the end of the procedure. The extremely variable function of the reexpanded lobe after lobectomy was striking. Function was well maintained after extrapleural pneumonolysis and extraperiosteal plombage. A marked decrease was observed only during manual depression of the lung or if the pleura was accidentally opened. A detailed analysis of the functional alterations during these operations will be presented in the near future.[19]

SUMMARY

Experiences with 1,000 bronchospirometric examinations were reviewed. Because of the unusual breathing conditions bronchospirometry should be used only as an adjunct to other pulmonary function studies.

The severity of resistance breathing with various double-lumen catheters was quantitated. Resistances varied not only from one type of tube to another but also between the two sides of the same tube. Obstruction offered by the catheters was many times larger than that offered by the normal human airways.

Oxygen breathing, another abnormal condition during bronchospirometry, was shown to have no effect on the ratio of oxygen uptake of the two lungs in normal individuals and in patients with only moderate unilateral pulmonary disease. Room air bronchospirometry showed that conventional oxygen breathing leads to overestimation of the functional participation of greatly damaged lungs.

Contraindications to the examination were discussed. Severe dyspnea did not preclude successful split function studies. An occasional adverse effect on the subsequent course of pulmonary tuberculosis was thought not to be due to the intubation itself but rather to retention of purulent material and implantation of bacillus laden secretions in previously unaffected parts of the lung. Excessive premedication, long lasting topical anesthesia and inadequate after care was shown to have been responsible for most febrile reactions and spreads after bronchospirometry.

Accurate information concerning functional distribution was obtained following 89 per cent of 724 examinations. No useful data were derived from 4 per cent of examinations. Incorrect positioning of the catheter was the most common cause of poor results. A procedure was outlined which should assure a maximal number of satisfactory studies.

Results of special tests including differential residual volume determination, differential analysis of distributional factors and pneumotachography of each lung were summarized. The outcome of bronchospirometry during exercise and during thoracic surgical operations was mentioned.

The author wishes to express his indebtedness to Dr. V. O. Bjork, Stockholm, Sweden; Dr. J. V. Maloney, Camp Lejeune, North Carolina; Drs. J. J. Cincotti and T. R. Watson, Jr., Rutland Heights, Massachusetts; and Drs. D. W. Cugell and W. E. Patton, Boston, Massachusetts, who participated in various phases of this investigation.

RESUMEN

Se revisa el resultado de la experiencia de 1,000 exámenes broncoespirométricos. Debido a las desusadas condiciones de la respiración la broncoespirometria debe emplearse solamente como adjunto de los otros procedimientos de estudio de la función pulmonar.

Se estima el grado de importancia de la resistencia respiratoria con varios catéteres de doble luz. Las resistencias variaron no solo de un tipo de tubo a otro sino de un lado a otro del mismo tubo. La obstrucción presentada por

los catéteres fué muchas veces mayor que la ofrecida por los conductos aereos normales.

La respiración de oxigeno, que es otra condición anormal durante la broncoespirometria, ha demostrado que no tiene efecto sobre la cantidad de oxigeno captado por los dos pulmones en individuos normales y en enfermos con la enfermedad unilateral y moderada. La broncoespirometria con el aire ambiente mostró que el uso del oxigeno como se acostumbra hacer conduce a una sobreestimación de la participación funcional de pulmones grandemente dañados.

Se discuten las contraindicaciones del examen. La disnea severa no impidió una separación satisfactoria de las funciones. Un efecto desfavorable en el curso ulterior de la tuberculosis, no se creyó debido a la entubación misma sino más bien a la retención de material purulento y a la implantación de secreciones cargadas de bacilos en areas antes no afectadas.

La excesiva premedicación, la anestesia local larga y el cuidado posterior al método cuando no es adecuado, se han mostrado responsables de las reacciones febriles y de las diseminaciones después de la broncoespirometria.

Se obtuvo exacta información respecto de la distribución funcional en 89 por ciento en 724 broncoespirometrias. No hubo datos útiles en 4 por ciento de los exámenes. La incorrecta colocación del catéter fué la causa más común de esta falla. Se detalla un procedimiento para asegurar el maximo de resultados satisfactorios.

Se resumen los resultados de pruebas especiales tales como la determinación diferencial del volumen residual, el analisis diferencial de los factores de distribución y la neumotacografía de cada pulmón. Se menciona el rendimiento de salida de la broncoespirometria durante el ejercicio y durante las operaciones quirúrgicas de torax.

RESUME

L'auteur décrit l'expérience qu'il a acquise à la suite de 1.000 examens bronchospirométriques. Etant donné les conditions inhabituelles de respirations, on ne devrait utiliser la bronchospirométrie que comme auxiliaire des autres études de la fonction pulmonaire.

L'auteur à calculé l'importance de la résistance que rencontre la respiration lorsqu'on utilise différents cathéters à double ouverture. Les résistancs varié non seulement d'un type à l'autre de tubes mais encore entre les deux extrémités du même tube. L'obstruction provoquée par les cathéters se montra souvent plus importante que celle qui provient des voies aériennes humaines normales.

La respiration d'oxygène qui réalise une autre condition anormale au cours de la bronchospirométrie se montra n'avoir aucun effet sur la quantité d'oxygène utilisée par les deux poumons chez les individus normaux et chez les malades qui n'étaient atteints que de localisations pulmonaires modérées et unilatérales. Les calculs bronchospirométriques avec respiration d'oxygène montrèrent que l'on surestimait la capacité fonctionnelle des poumons gravement atteints.

L'auteur discute les contre-indications de cet examen. Une grande dyspnée

n'empêche pas des études fonctionnelles parfaitement précises. La possibilité d'effets de'favorables sur l'évolution d'une tuberculose pulmonaire n'a pas semblé être due à l'intubation elle-même mais plutôt à la rétention d'éléments purulents, et à la dissémination de sécrétions bacillifères dans des parties du poumon restées jusque là saines. Il semble que l'excès de traitements préopératoires, l'anesthésie locale trop longue, des soins postopératoires malencontreux, furent responsables dans la plupart des cas, des réactions fébriles et des ensemencements bacillifères après la bronchospirométrie.

Des renseignements parfaitement valables concernant l'état fonctionnel furent obtenus dans 89% sur 724 examens pratiqués. Des renseignements sans intérêt furent la conséquence de 4% des examens. La cause la plus habituelle des mauvais résultats fut l'utilisation incorrecte de la sonde. L'auteur à décrit un procédé qui permettrait un nombre beaucoup plus élevé de résultats satisfaisants.

Il à résumé les résultats de tests particuliers parmi lesquels la détermination du volume résiduel différentiel et l'annalyse différentielle des facteurs de distribution et de la pneumotachygraphie de chaque poumon. Il fait mention des résultats de la bronchospirométrie au cours des exercices et au cours de la chirurgie thoracique.

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Isonicotinic Acid Hydrazide (Rimifon) in the Treatment of Tuberculosis

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Following reports on the effectiveness of isonicotinic acid hydrazide in the treatment of tuberculosis,[1] a clinical trial was instituted at the San Angel Sanatorium in Mexico City. Beginning in March 1952, a series of 13 hospitalized and 12 ambulatory patients were started on therapy with Rimifon* and the results evaluated at the end of a 90-day period.

The hospitalized patients selected for study were those known to be resistant to streptomycin and para-aminosalicylic acid, in whom all other procedures, medical and surgical, had been found ineffective. In addition, these patients were under observation for many months and in each instance, there was no evidence of spontaneous improvement. Throughout the study an attempt was made to maintain the same circumstances of environment, rest, and food as during the previous therapeutic regime, except that increased food allowance was provided if specifically requested by the patient. No other medication was administered.

The ambulatory group was composed chiefly of former patients of the Sanatorium having less serious infection who were observed weekly in the clinic.

The following procedures were carried out for critical evaluation of the effects of therapy:

Roentgenograms: Previous roentgenograms were reviewed and a new film was taken prior to instituting therapy. Fluoroscopy was done weekly and a film made every 30 days. Tomograms were taken when necessary.

Hematology: Hematologic examination was made monthly of erythrocytic and leukocytic changes.

Sputum Examination: Prior to treatment with isoniazid, examination was made to confirm resistance to streptomycin and para-aminosalicylic acid. Culture of the Mycobacterium in sputum obtained by concentration or gastric lavage was made before treatment and at 30-day intervals.

Biochemical Examination: Sedimentation rate and determination of albumin-globulin ratio in the blood were regularly performed. Tests for liver and kidney function, and urine analyses, were made at the start of the study and repeated as necessary during the course of treatment.

Clinical observations were made daily.

The dosage used in this series, with one exception, was 4 milligrams per kilogram of body weight per day throughout the 90-day period. Adminis-

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Read at Meeting of the Academy of Medicine of Mexico, June 25, 1952.

*Rimifon (Isonicotinic Acid Hydrazide, Isoniazid) was supplied through the courtesy of Dr. Elmer L. Sevringhaus of Hoffmann-La Roche and grateful acknowledgment is made to him and to Dr. Irving Selikoff of Sea View Hospital, Staten Island, New York, for counsel in conducting this study.

tration was oral, in three divided daily doses. This dosage regime was utilized on the basis of the early experiences reported.[2] It might be noted parenthetically, however, that higher dosage ranges may be, and probably

TABLE I

Patient	Pulmonary Disease	Sputum Culture♦ Before Treatment	Sputum Culture♦ After 90 Days	Clinical▲ Results
C.E.*	Far advanced tuberculosis, bilateral; 1 cavity on right, 2 on left. Lower left lobectomy, upper left subsegmental resection. Multiple broncho-pleural-cutaneous fistulae.	positive	negative	very good
V.A.*	Spread to right lung after pleuropneumonectomy for destroyed left lung.	positive	persistently negative	very good
B.	Caseous pneumonic, extensive bilateral cavities.	positive	positive	very good
H.A.	Bilateral multiple cavities, 3 in left lung, 1 in right. Extrapleural apicolysis with Ivalon filling on left; wax plombage on right. Cavity open.	positive	alternating	very good
G.T.*	Pneumonic contralateral spread after left pleuropneumonectomy.	positive	negative	very good
R.G.*	Bilateral cavities. Pneumoperitoneum ineffective.	positive	positive	good
Re	Fibrocaseous, bilateral acvities. Thoracoplasty ineffective.	positive	positive	good
G.M.	Far advanced tuberculosis, bilateral extrapleural pneumothorax, bilateral open cavity.	positive	negative	good
G.C.	Bilateral excavated tuberculosis; extrapleural pneumothorax on left; intrapleural pneumothorax on right. Cavity open.	positive	positive	good (reoperated)
C.M.	Bilateral tuberculosis; extrapleural empyema and cutaneous fistulae. Thoracoplasty.	positive	positive	good
R.V.	Residual bronchiectasis after thoracoplasty.	positive	negative	good
R.**	Fibrocaseous bilateral far advanced tuberculosis.	positive	positive	poor
A.	Intrapleural empyema post pneumothorax.	negative	negative	poor (operated)

*See detailed case report.

**Patient died after 150 days' therapy.

♦Sputum results: 1 negative : remained negative.
5 positive : converted to negative.
6 positive : remained positive.
1 positive : now alternating.

▲Clinical response: 5 very good, 6 good, 2 poor.

should be, utilized. In one patient not responding satisfactorily at 4 milligrams per kilogram, the dose was increased to 8 milligrams per kilogram daily and maintained without toxicity for over 90 days.

Results

The degree of clinical improvement in the hospitalized group achieved at the end of the 90-day period, and the effect on sputum are recorded in Table I. The weight gain, effect on temperature, and sedimentation rate

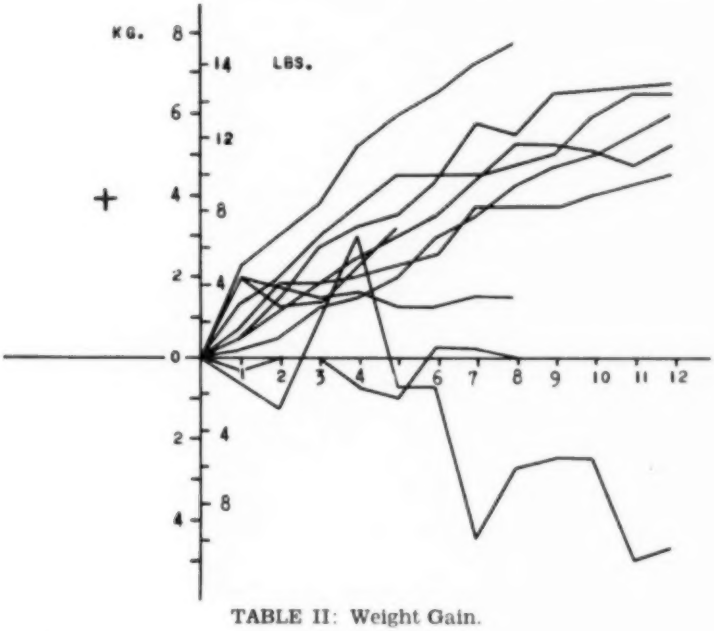

TABLE II: Weight Gain.

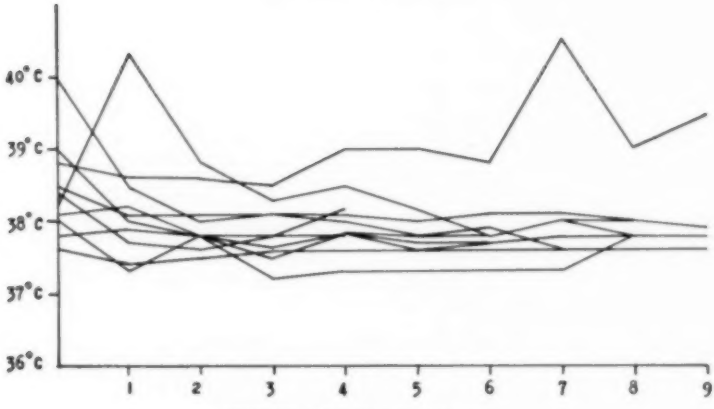

TABLE III: Temperature.

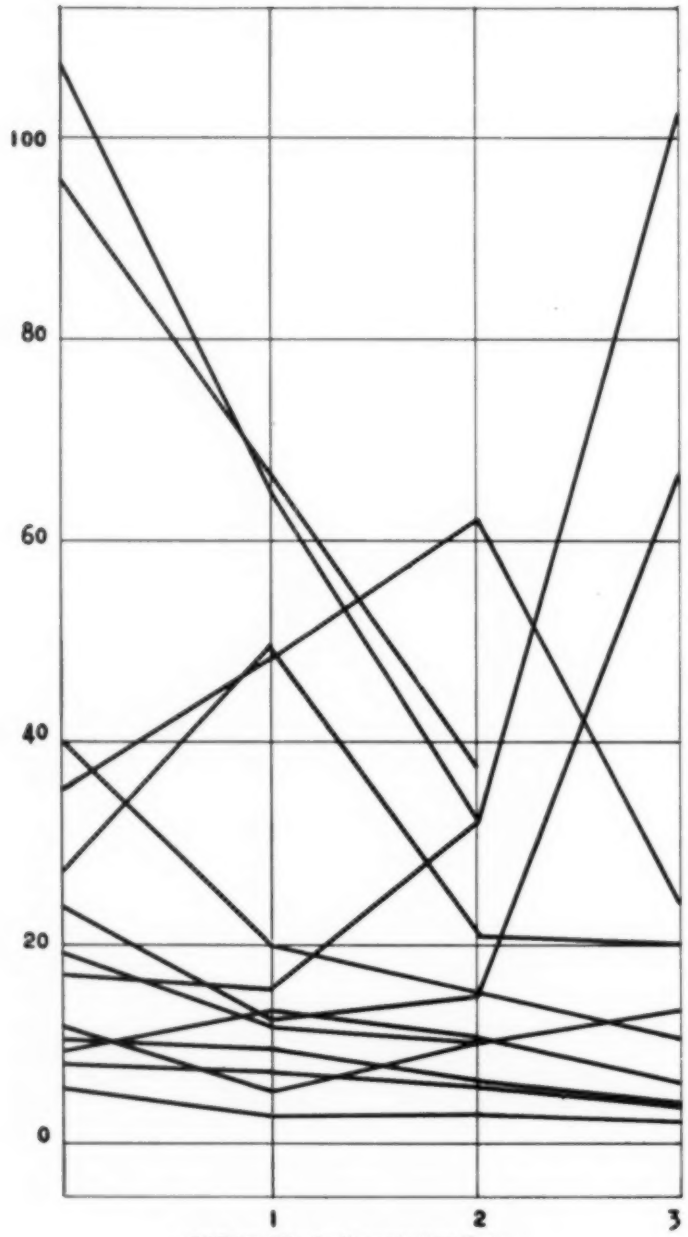

TABLE IV: Sedimentation Rate.

are shown graphically in Tables II, III and IV. Detailed case histories of four patients are included.

Clinical Response: Clinical improvement as evidenced by symptomatic response and physiologic control of the disease process was considered very good in five of the 13 patients. In six the response was considered good, and in two poor.

Effect on Sputum: The sputum was modified very rapidly in its appearance, becoming thinnish, less purulent and less abundant. The bacterial count diminished in most cases. In five out of 12 instances where the count was positive at the start of treatment the sputum became negative. In one patient the count alternated throughout the 90-day period. In six no reversal was obained. The one patient who had a negative count at the start remained negative throughout treatment.

The studies on the possibility of pre-existing, or emergence of, resistant strains to isonicotinic acid hydrazide indicated that one patient in the series had resistant strains prior to Rimifon therapy. In the other patients no resistant strains were found in the positive cultures taken at the beginning or at the end of the 90-day period.

Effect on Weight and Appetite: Ten of the 13 patients gained weight; in two as much as 2-kilogram increase occurred by the end of the first week of therapy. The gain in the others was less rapid but consistent. Failure of weight increase occurred in three patients. There was intercurrent empyema in one, and surgery in the other two. Increase in appetite was correlated with the weight gain, the increase in food consumption amounting to approximately 25 per cent of the former intake. It was the policy not to encourage the patients to eat but rather to observe their spontaneous reaction and to await request for further food allowance.

Effect on Temperature: In this series there was no patient having unusually high temperatures, although the group represented the most seriously afflicted patients in the sanatorium. As illustrated in Table III the trend was toward development of normal temperatures, except in the three instances where complications occurred as noted above.

Effect on Blood: Except in the patients with complications a general tendency toward increase in *erythrocytes* was noted. This experience with *isoniazid* is in contrast to the reported observations of Selikoff, Robitzek and Ornstein,[3] who found that treatment with *iproniazid* tended to depress hemoglobin levels. The *leukocyte* count either decreased toward normal or rose to normal in those patients who had low counts. In four patients neutrophils persisted around 80 per cent, but in the others they tended to group around 50 to 60 per cent. On the contrary, there was a definite tendency for the *lymphocytes* to increase and for the *monocytes* to diminish; the *eosinophils* showed a variable tendency to increase. The sedimentation rate approached normal values.

Case Histories

The small number of cases studied in this series does not provide statistically significant data for determining the possibilities of the drug. How-

ever, the cases detailed below afford information on isoniazid therapy in critically ill patients.

Case V.A.: Female, age 23 with caseous pneumonia on the left side, was found to have an active and destructive form of pulmonary tuberculosis. On admittance the x-ray film showed a typical "destroyed lung." In the right lung only small congestive shadows were evident (Figure 1). Streptomycin and para-aminosalicylic acid had been given for two months without response. Transfusions, pneumoperitoneum and other measures were employed to prepare the patient for left pleuropneumonectomy. Following operation a flare-up of infection occurred and streptomycin and para-aminosalicylic acid were again administered although resistance was suspected, which was later confirmed. Sulfoxone sodium was then tried and slight improvement took place in the ensuing two weeks. After that time deterioration was rapid and appetite completely disappeared. She then weighed 86 lbs., pulse was 110 to 120 and maximum temperature 99.5 degrees F. Status at this time is shown in Figures 2 and 3. It became necessary to force feed through a gastric catheter. Isoniazid therapy was started administering 4 mg./kg daily. Spectacular improvement was observed from the second day. Appetite reappeared with corresponding steady increase in weight amounting to 7 kg. by the end of 90 days. Cough and expectoration diminished and the sputum became whitish. Sputum cultures alternated between positive and negative. Temperature soon became normal. The blood count at the beginning of treatment and after 90 days was as follows:

	Before	After
Erythrocytes	4,050,000	5,500,000
Hb per cent	76	100
Leukocytes	7,550	10,700
Lymphocytes	7	33
Monocytes	11	3
Neutrophils	82	62
Eosinophils	0	2
S. R. Westergren	18.5	13
L/M Ratio	1½ : 1	10 : 1
Weight	39,000 Gm.	46,000 Gm.

Roentgenograms after 90 days and tomograms at monthly intervals indicated decrease in the lesions; the cavity visible at the tomograph detail decreased from 1 cm. in diameter to 4 mm. in the second film (Figure 4). At the start of treatment the patient became euphoric and remained so.*

Case G.T.: A 33-year old female who had developed tuberculosis postpartum came to the sanatorium following treatment at another institution, including intrapleural pneumothorax and a Jacobaeus operation. She was found to have a broncho-cavito-cutaneous fistula, as the large cavity opened through a fistula to the skin (Figure 5, x-ray film of the lung after expansion). A pleuropneumonectomy without thoracoplasty was performed and one month later caseous

*Further observation, 90 days after the initial three months therapy, shows continued steady improvement. The sputum has remained consistently negative (culture) and the gain in weight after 180 days is 17 Kg. Roentgenograms also confirm definite improvement (October 3, 1953). At the end of therapy with Rimifon, the drug was discontinued with optional results (April, 1953).

empyema developed. Following curettage of the space thoracoplasty was done and flaps were tailored to fill the space. There was immediate benefit on the operated side but she developed pneumonic contralateral basal spread of the pneumonic type (Figure 6). Her condition was critical at the time isoniazid was started. Gradual improvement occurred, and after 10 days oxygen was withdrawn, the basal shadow disappeared and she entered a frank recovery (Figure 7). Obviously a gain in weight could not be expected during this period; actually the patient lost 5 kg. although definite improvement had occurred.

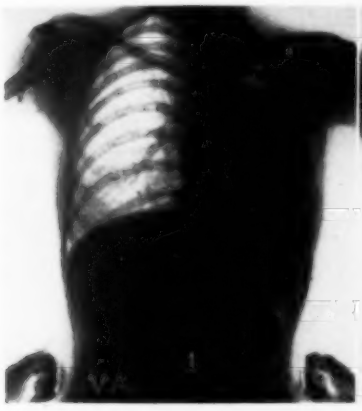

FIGURE 1

FIGURE 2

Figure 1, Case V.A.: Destroyed left lung. Status prior to pleuropneumonectomy.
Figure 2, Case V.A.: After left pleuropneumonectomy. Spread to right lung.

FIGURE 3

FIGURE 4

Figure 3, Case V.A.: Tomographic detail showing cavity in remaining lung, prior to isoniazid therapy.—*Figure 4, Case V.A.:* Tomographic section showing marked decrease in cavity size after 90 days therapy. Further observation showed disappearance of cavity.

FIGURE 5 FIGURE 6 FIGURE 7

Figure 5, Case G.T.: Status prior to therapy, with broncho-cavito-cutaneous fistula.
Figure 6, Case G.E.: Spread to right base with post pleuro-pneumonectomy empyema.
Figure 7, Case G.T.: Clearing of spread with isoniazid therapy.

The blood cells before and after 90 days of isoniazid were:

	Before	After
Erythrocytes	4,630,000	4,850,000
Hb per cent	72	76
Leukocytes	9,500	5,400
Lymphocytes	20	25
Monocytes	8	2
Neutrophils	72	72
Eosinophils	1	1
S. R. Westergren	35.5	22.5
L/M Ratio	2.5 : 1	12 : 1

Case C.E.: A 35-year old man, with a history of pulmonary tuberculosis for 18 years, on entrance had far advanced bilateral tuberculosis. The tomograms showed one cavity on the left lower lobe and one cavity in the posterior segment; through the laminograph another cavity was visible on the right side. Following the use of all available measures including streptomycin and para-aminosalicylic acid to which resistance developed, a lower lobe lobectomy and wedge resection of the left upper lobe was performed. Multiple broncho-pleural-cutaneous fistulae developed and his condition gradually deteriorated until he was semidelirious, had marked anemia and was in a state of extreme prostration (Figure 8). Isoniazid was administered with dramatic results; he became alert, euphoric and developed good appetite. One month later improvement was great enough to permit a second lobectomy of the upper lobe and thoracoplasty at the same stage, a surgical procedure which took five hours and required 7 liters of blood transfusions (Figure 9). Following the operation he developed anuria for three days and isoniazid therapy was discontinued. He gradually reverted to normal within 10 days, and administration of the drug was resumed without further incident.

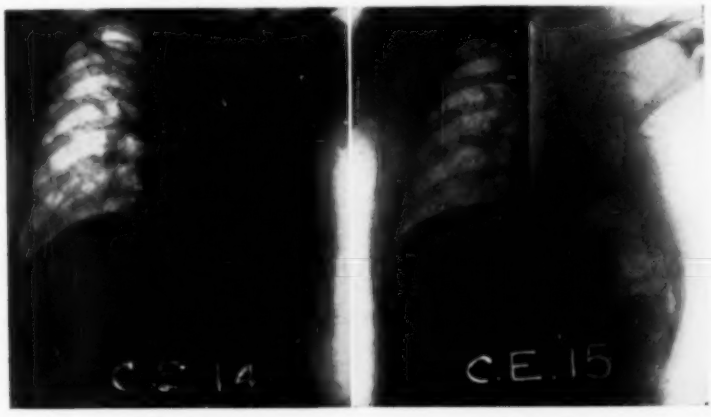

FIGURE 8 FIGURE 9

Figure 8, Case C.E.: Extensive bilateral disease in moribund patient.—*Figure 9, Case C.E.:* After excisional surgery, made possible by clinical improvement with isoniazid therapy.

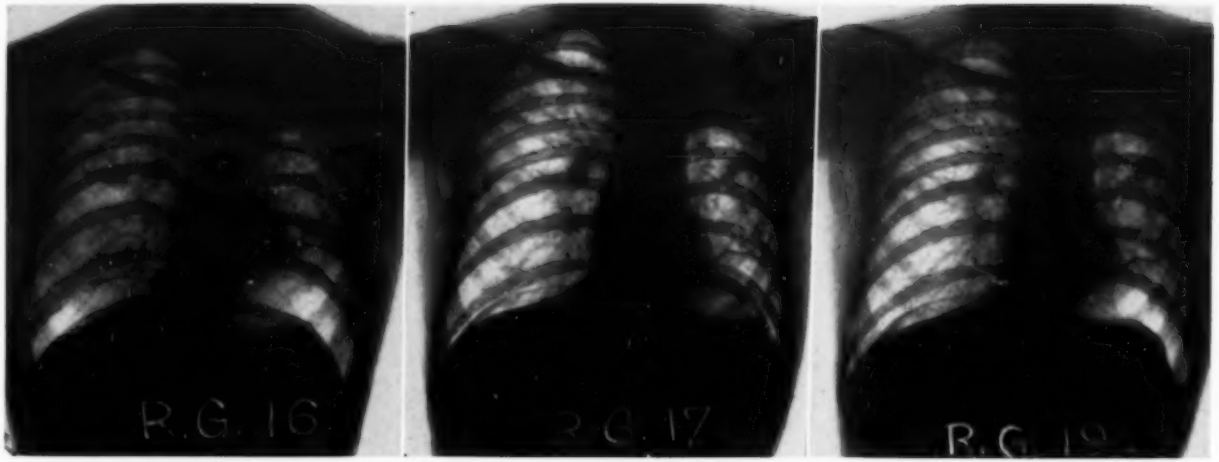

FIGURE 10 FIGURE 11 FIGURE 12

Figure 10, Case R.G.: Bilateral cavities at onset of isoniazid therapy.
Figure 11, Case R.G.: X-ray improvement after two weeks of isoniazid therapy.
Figure 12, Case R.G.: X-ray after three months of isoniazid therapy.

Case R.G.: A young man who three years previous to admission had undergone extrapleural pneumothorax elsewhere for treatment of active tuberculosis, was found to have bilateral cavities, one at the left upper lobe, obviously pre-existing to the extrapleural and the other in the right lung (Figure 10). Pneumoperitoneum on both sides was started without effect. Isoniazid was then administered in a dosage of 4 mg./kg. daily and after two weeks x-ray film improvement was noted (Figure 11). A tomogram four days later demonstrated that although the cavity existed, the size was much smaller i(Fgure 12). After three months' treatment no cavity was visible on the conventional x-ray film although the tomograph still showed a small cavity. While the sputum remained positive, the bacillary count dropped sharply. An increase in weight occurred. The blood picture was as follows:

	Before	After
Erythrocytes	4,020,000	4,700,000
Hb per cent	78	96
Leukocytes	6,400	7,400
Monocytes	3	3
Neutrophils	58	63
Eosinophils	6	10
Lymphocytes	32	23
S. R. Westergren	16.25	32.5

In the ambulatory patients results were much less favorable. In only three of 12 was the sputum converted to negative, weight gain was less consistent, and in only one patient was roentgenologic improvement noted. This experience emphasizes the need for hospitalization and the usual controlled regime as concomitant measures with drug therapy.

SUMMARY

An investigation has been carried out to determine the efficacy of isoniazid (Rimifon) in a series of 25 tuberculous patients. Beginning in March 1952, 13 were maintained under sanatorium regime and 12 were ambulant cases seen at the out-patient service of the San Angel Sanatorium in Mexico City.

Clinical trial over a 90-day period indicates that the drug is almost non-toxic in human beings at a daily dosage of 4 milligrams per kilogram of body weight. Further clinical observations in one patient using a routine dosage of 8 milligrams per kilogram of body weight for a period longer than 90 days, seem to indicate that the drug is also well tolerated on this higher dosage schedule. The drug was noted to produce a marked euphroic effect.

In the hospitalized group symptomatic response in the majority of patients was excellent as evidenced by increase in appetite, rapid gain in weight, tendency toward normal temperature, diminished cough and improved character of the sputum.

In only five of the 12 hospitalized cases with positive sputum cultures at the beginning of therapy were consistently negative cultures obtained by the end of the treatment period.

The hematological changes are consistent with the shifting of the immunobiological response of the body to the tuberculous infection.

Roentgenological changes were slow in developing in the few cases in which they were evident. Examination of the films taken at the end of 90 days of treatment shows the beginning of change in some of the cases not previously exhibiting an improvement.

Some patients completely failed to respond to the drug. There is the possibility of a correlation between failure to respond to isoniazid and previous history of spontaneous or acquired resistance to chemically related drugs such as the thiosemicarbazones.

The results in the ambulatory patients in the series were less satisfactory indicating the need for bed rest and an adequately controlled regime in the treatment program.

In evaluating these results consideration should be given to the fact that in this series the hospitalized patients had not responded to any other procedures and were critically ill at the time treatment was started. Four of the patients were practically moribund and in three of these cases the drug proved to be life-saving. The fourth patient responded initially but then regressed. It was felt that her life was prolonged about four months because of the drug. While uniform results were not obtained so far as the degree of response is concerned, isoniazid provided a most effective therapy for the severely ill tuberculous patients in the series.

RESUMEN

Se llevó a cabo una investigación para determinar la eficacia de la isoniacida (Rimifón) en una serie de veinticinco enfermos de tuberculosis. Principiando en Marzo de 1952 trece de ellos, se mantuvieron bajo régimen sanatorial y doce, eran casos ambulatorios del servicio de externos del Sanatorio San Angel de México.

El estudio clínico por un período sobrepasando noventa días, indica que la droga casi no es tóxica en los seres humanos a la dosis de cuatro miligramos por kilo de peso. Una observación ulterior en un enfermo con ocho miligramos de Rimifón por kilo de peso por un período mayor de noventa días, parece indicar que la droga es también tolerada con esta dosis mayor.

Se notó que la droga produce efectos eufóricos marcados.

En el grupo hospitalizado la respuesta sintomática en la mayoría de los enfermos, fué excelente, según lo demuestran el aumento de apetito, el rápido aumento de peso, la tendencia a la normalización de la temperatura, disminución de la tos y la mejoría del aspecto del esputo.

En sólo cinco de los doce hospitalizados con cultivos positivos de los esputos al principio del tratamiento, se obtuvieron cultivos de esputos negativos al fin del tratamiento.

Los cambios hematológicos, están de acuerdo con los que ocurren cuando hay alteraciones inmunobiológicas favorables en la infección tuberculosa.

Los cambios roentgenológicos fueron lentos en los pocos casos en que fueron evidentes. El examen de las películas tomadas al fin de los noventa

días, mostraron el principio de un cambio en algunos casos que no habían mostrado previamente mejoría.

Algunos enfermos dejaron de responder completamente a la droga. Hay una posibilidad de correlación entre la falta de respuesta a la isoniacida y un antecedente de resistencia adquirida a drogas emparentadas químicamente tales como las tiosemicarbazonas.

Los resultados en los enfermos ambulatorios en esta serie fueron menos satisfactorios, lo que indica la necesidad del reposo en cama así como un régimen de control adecuado para el plan de tratamiento.

Para la valuación de estos resultados debe tenerse encuenta que en esta serie, los pacientes hospitalizados no habían respondido a ningún procedimiento y se encontraban muy gravemente enfermos cuando se inició el tratamiento. Cuatro de los enfermos, se encontraban prácticamente moribundos y en tres de éstos, la droga verdaderamente les salvó la vida. El cuarto enfermo respondió inicialmente, pero después continuó su evolución hacia la muerte. Se considera sin embargo, que el uso de la droga, prolongó su vida aproximadamente por cuatro meses.

Si bien no se obtuvieron resultados uniformes en lo que se refiere a la respuesta, la isoniacida, demostró ser un recurso terapéutico de lo más útil en esta serie de pacientes.

RESUME

L'auteur rapporte l'étude qu'il a pu faire pour déterminer l'action de l'isoniazide dans un groupe de 25 tuberculeux. 15 d'entre eux furent maintenus au régime sanatorial et douze furent suivis ambulatoirement à la consultation du Sanatorium St-Angel à Mexico. L'experience a ete commence dan Mars 1952.

L'expérimentation poursuivie pendant 90 jours montre que ce produit est à peu près atoxique chez l'homme à los dose de 4 mmgr. par kilogramme. Des observations ultérieures portant sur un malade utilisant un dosage habituel de 8 mmgr. par kilogramme pendant plus de trois mois, semblent montrer que le produit est toléré même à hautes doses. On a remarqué qu'il déterminait un effet euphorique notable.

Parmi les malades hospitalisés, dans la majorité des cas, l'action fut excellente, marquée par l'accroissement de l'appétit, l'augmentation rapide du poids, la tendance à la disparition de la fièvre, la diminution de la toux, et l'amélioration de l'expectoration.

Ce n'est que chez un des douze malades hospitalisés que des cultures de crachats positives au début furent négativées d'une façon nette à la fin du traitement.

Les modifications hématologiques sont constantes; on note une transformation des résultats des examens biologiques.

Les modifications radiologiques ne se développèrent que lentement dans le nombre restreint de cas où elles furent effectivement constatées. L'examen des radiographies prises à la fin de trois mois de traitement montra que des modifications apparaissaient dans certains des cas qui n'avaient pas paru primitivement améliorés.

Pour certains malades, il y eut un échec complet du traitement. On peut peut-être envisager que ces cas appartiennent à des formes avec résistance spontanée ou acquise au traitement chimique, comme on peut le constater avec les thiosemicarbazones.

Les résultats, chez les malades qui avaient été traités ambulatoirement, furent moins satisfaisants. Ils montrent la nécessité du repos intégral, et du contrôle médical strict du traitement.

Lorsqu'on évalue l'importance de ces résultats, il faut tenir compte que les malades hospitalisés, traités par l'isoniazide, n'avaient pas répondu favorablement à tout autre procédé thérapeutique, et que leur état était tout à fait critique lors de la mise en route du traitement. Quatre des malades étaient pratiquement mourants, et chez trois d'entre eux, le remède sembla véritablement leur avoir sauvé la vie. La quatrième malade fut au début améliorée, mais cette amélioration ne se maintint pas. On peut estimer cependant que sa vie fut prolongée de quatre mois environ, grâce à cette drogue.

Bien que les résultats ne furent pas tout à fait comparables, l'isoniazide dans l'ensemble se montre une thérapeutique très efficace chez les tuberculeux sévèrement atteints.

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Experimental Bacterial Endocarditis and Proliferative Glomerulonephritis

Description of Method of Production Utilizing Bilateral Lower Extremity or Single Aorta-Vena Cava Arteriovenous Fistulas*

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In previous experimental studies reported[1,2] from this laboratory, we have observed that increasing the work of the heart in dogs by means of large arteriovenous fistula loads has caused a profound increase in the susceptibility of these animals to the development of a persistent septicemia with a predilection of the bacterial organisms or their products for the valve leaflets and the renal glomeruli. As a result, a number of these dogs with large arteriovenous fistula loads have "spontaneously" developed and succumbed to vegetative endocarditis with severe valvular destruction without the intentional introduction of any bacteria into the animals' bodies. In addition, some of these same animals with endocarditis have also developed an acute diffuse proliferative glomerulonephritis. Figure 1 depicts the valvular pathology in one of these dogs dying of endocarditis "spontaneously" acquired secondary to large arteriovenous fistulas.

The mechanism of the occurrence of this "spontaneous" bacteremia and consequent endocarditis and glomerulonephritis in the dogs with large arteriovenous fistulas would appear to depend upon the fact that the cardiovascular stress engendered by the shunts sets in motion certain mechanical and endocrine alterations which result in a significant and specific increase in the susceptibility to bacterial infection of the endothelial surfaces of the heart and kidneys. This increase in susceptibility is so great that the animals can acquire their septicemia from the relatively few micro-organisms which gain entrance into their blood streams by adventitious routes. This fortuitous entrance of bacteria through skin or intestinal mucosal abrasions into the blood stream no doubt occurs in most animals from time to time, but under normal conditions no growth or localization of the bacteria occurs since the normal body defenses readily destroy the organisms.

This theory as to the origin of the bacteremia in these animals with large shunts appears to be further supported by our subsequent experience

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**U.S.P.H.S. Senior Post-doctorate Research Fellow.

FIGURE 1

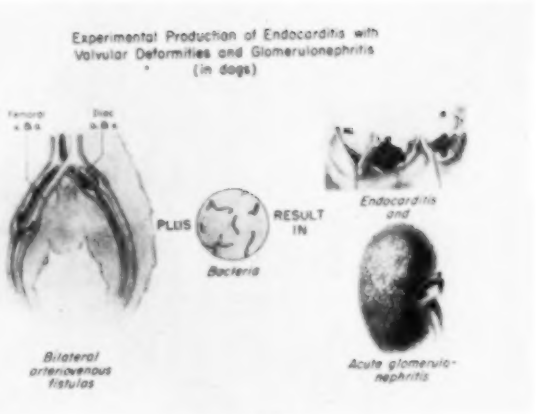

FIGURE 2*

Figure 1, Dog 226. Aortic Valve Endocarditis: Pseudomonas aeruginosa bacteremia occurring without the intentional injection of bacteria. Death occurred 112 days after construction of bilateral arteriovenous fistulas between iliac vessels on one side and the femoral vessels in opposite leg. *Note:* The soft, friable vegetations on all cusps typical of bacterial endocarditis.—*Figure 2*:* Experimental Method Utilizing Bilateral Arteriovenous Fistulas.

*Reproduced from Arch. Surg., 63:421-434, 1951, by Permission.

which has indicated that the spontaneous occurrence of bacteremia and endocarditis in dogs with large arteriovenous fistulas may be delayed in most instances for long periods of time if meticulous efforts are made to control the introduction of bacteria through adventitious routes, particularly through the skin and through the mucous membranes of the gastrointestinal tract by such methods as frequent deworming (to prevent intestinal abrasions due to parasites), the frequent application of a parasiticide to the skin, and the avoidance of vena punctures. However, in these animals with large arteriovenous fistulas, their susceptibility to bloodstream infection by bacteria deliberately introduced is in no way diminished by the passage of time as is attested to by the occurrence of a fulminating endocarditis and death following the introduction of small numbers of bacteria which are innocuous to normal dogs.

Further investigations of the mechanism responsible for these observations has substantiated the existance of a fundamental relationship between the effects of a systemic cardiovascular stress, such as arteriovenous fistulas, and increased susceptibility of the heart valves and kidney glomeruli to bacterial infection or the products of bacterial infection. This relationship as derived from our previous studies,[1,2] is expressed in Table I.

On the basis of these initial observations, experimental methods have been developed for the production of endocarditis and diffuse proliferative glomerulonephritis (Figures 2 and 3). The first of these methods utilizes the cardiovascular stress of bilateral arteriovenous fistulas in the lower extremities as depicted in Figure 2 together with the intravenous injections of relatively small numbers of bacteria. Subsequent experience has also indicated that a single aorta-vena cava fistula may be utilized, as portrayed in Figure 3, in place of the bilateral iliac and femoral arteriovenous fistulas with equally consistent results in the regular production of endocarditis.

The immediate practical significance of this concept has been to establish a reliable and effective method for the experimental production and study of endocarditis and glomerulonephritis in a readily available animal such as the dog. Our observations upon the use of this method for the production of endocarditis and glomerulonephritis are described in greater detail herein.

TABLE I

THE RELATIONSHIP BETWEEN ARTERIOVENOUS FISTULA LOADS AND SUSCEPTIBILITY TO BACTERIAL ENDOCARDITIS IN DOGS*

Arteriovenous Fistula Load	
Very Susceptible to Endocarditis	Less Susceptible to Endocarditis
One Iliac and One Femoral *or* Two Iliacs *or* Aorta-Vena Cava	Bilateral Femoral *or* One Iliac *or* One Femoral

*Young Adult Age (2 to 5 Years).

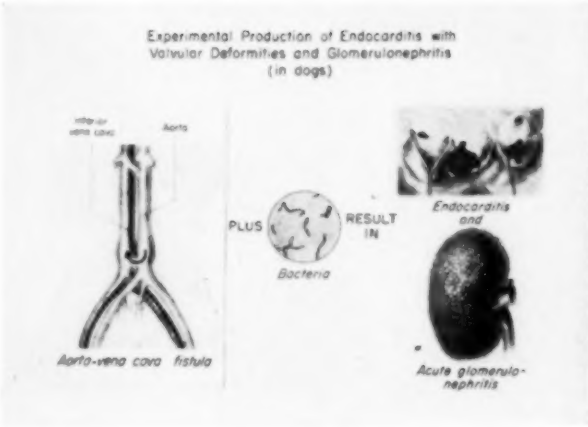

FIGURE 3

FIGURE 4

Figure 3: Experimental Method Utilizing Aorta-Vena Cava Arteriovenous Fistula.—*Figure 4, Dog 1345. Mitral Valve Endocarditis:* Produced by method depicted in Figure 2 utilizing 0.05 ml. of a 24-hour broth culture of beta hemolytic streptococcus injected intravenously once daily for seven days. *Note:* Ulcerative bacterial vegetation with perforation of leaflet.

Plan of Experiments

Below are listed four groups of dogs which have been used in these experiments. The incidence of endocarditis in each of these groups has been determined by careful gross observation of the heart at autopsy together with microscopic study of sections from each of the 53 animals. The incidence of glomerulonephritis has been determined by microscopic study of kidney sections made from each animal.

Group 1: Nineteen Dogs With Bilateral Lower Extremity Arteriovenous Fistulas Receiving Intravenous Injections of Beta Hemolytic Streptococci (Lancefield Group D, "Strain I. F.") subdivided as follows on the basis of the number of bacteria injected:

Group 1A: Seven Dogs Receiving 0.005 ml. Intravenously per Day of the 24-hour Broth Culture for five to seven Days.

Group 1B: Six* Dogs Receiving 0.05 ml. Intravenously per Day of the 24-hour Broth Culture for seven Consecutive Days.

Group 1C: Six Dogs Receiving 0.5 ml. per Day of the 24-hour Broth Culture for seven Consecutive Days.

Group 2: Seven Dogs With a Single Aorta-vena Cava Arteriovenous Fistula Receiving Intravenously Either "Strain I. F." of the Beta Hemolytic Streptococci (Lancefield Group D) or Type XIV of the Beta Hemolytic Streptococci (Lancefield Group A).

Group 3: Ten Dogs With One Femoral Arteriovenous Shunt Receiving Intravenous Injections of Beta Hemolytic Streptococci. (Group D, "Strain I. F.").

Group 4: Seventeen Normal Dogs (Controls) Receiving Intravenous Injections of the Same Bacteria Used in the Experiments of Groups 1, 2 and 3.

Bacteriological Data

In the animals of Groups 1, 2, 3, and 4, described above, a temporary bacteremia was produced by the intentional intravenous injection of one or the other of the two bacterial strains described below:

"Strain I. F." which has been identified as a Lancefield Group D strain of hemolytic streptococcus with the beta type of hemolysis. This organism, originally chosen at random from a hospital laboratory for use in these experiments, had been isolated from a patient† with cholangitis and hepatic abscesses due to a malignant obstruction of the common bile duct. The colony count of a 24-hour trypticase-soy†† broth culture of this organism ranged from 1,290,000,000 to 2,450,000,000 organisms per ml. with a mean of about 1,500,000,000 per ml.

The other bacterial strain††† utilized in these experiments was a Type XIV, beta hemolytic streptococcus of the Lancefield Group A. This organism was cultured on a brain heart infusion media†††† and the colony count

*One dog in this group received 0.05 ml. per day for seven consecutive days of Type XIV, Beta Hemolytic Streptoccus (Lancefield Group A) instead of the "Strain I. F." (Lancefield Group D).

†I. F., U.H. No. 817510.

††Baltimore Biological Laboratory, Baltimore, Maryland.

†††We are indebted to Dr. W. W. Spink, Department of Medicine, University of Minnesota Medical School for providing both of these organisms.

††††Difco Laboratories, Detroit, Michigan.

TABLE II: PRODUCTION OF ENDOCARDITIS IN DOGS WITH BILATERAL* ARTERIOVENOUS FISTULAS

Beta Hemolytic Streptococcus (Lancefield Group D) 0.005 Ml. per Day†

		— — ARTERIOVENOUS FISTULAS — —			INTRAVENOUS DOSE OF 24-HR. BROTH CULTURE**			
Dog No.	Sex and Wt., Kg.	Location	Length mm.	Duration at Start of Bacterial Injections Days	Ml./Day	No. Days	Results	Heart Valves Involved
193	M, 11.6	Iliac Femoral	24 27	68 53	0.005	5	Sacrificed, Normal Heart and Kidneys	—
205	M, 11.1	Iliac Femoral	23 26	74 61	0.005	5	Sacrificed, Normal Heart and Kidneys	—
178	M, 13.8	Iliac Femoral	26 25	75 58	0.005	5	Sacrificed, Normal Heart and Kidneys	—
200	F, 19.8	Iliac Femoral	27 25	95 164	0.005	5	Died of Bacterial Endocarditis 31 Days After First Injection of Bacteria	Mitral
139	F, 8.4	Iliac Femoral	17 15	16 18	0.005	7	Sacrificed, Negative Heart and Kidneys	—
194	F, 9.0	Iliac Iliac	16 20	35 32	0.005	7	Sacrificed, Bacterial Endocarditis and Proliferative Glomerulonephritis	Mitral
196	M, 12.8	Iliac Femoral	20 24	183	0.005	7	Died of Bacterial Endocarditis 59 Days After First Injection of Bacteria	Mitral, Aortic

*An iliac arteriovenous fistula in one leg, and an iliac or femoral arteriovenous shunt in the other leg.
**Average colony count per milliliter of a 24-hr. broth culture of this strain = 1,500,000,000 organisms.
† = Animals of sub-group 1A in text.

No. of dogs with fistulas injected = 7
No. of dogs with endocarditis = 3
No. of dogs with proliferative glomerulonephritis = 1

of a 24-hour culture ranged from 50,300,000 to 65,500,000 with a mean of about 60,000,000 per ml.

All of the bacterial injections in these series of dogs were made intravenously using sterile syringes and a preparation of the skin as indicated below for blood cultures. An injection of 0.05 ml. or 0.005 ml. of a 24-hour broth culture was made by diluting 1.0 ml. of the 24-hour culture to 10 ml. or to 100 ml., respectively, with normal saline, and then injecting 0.5 ml. of the resulting dilution.

The blood cultures were made at frequent intervals by withdrawing 10 ml. of blood from the jugular vein into a sterile syringe after preparation of the skin using the following routine: shaving the hair, soap and water, sterile saline rinse, and then tincture of Zephiran (1:1000). One-half of this blood was placed in broth and the other half into 3.5 per cent sodium citrate solution for use in making pour plates for colony counts. The number of organisms per ml. of blood was roughly quantitated for all positive cultures.

Experimental Procedures

All of the animals used in these studies were young adult dogs of either sex, previously dewormed,* immunized against distemper,** dipped in a parasiticide,*** and acclimated to the animal colony for a period of four weeks before use. All dogs were fed daily a diet consisting of standard dog biscuits supplemented with fresh horsemeat and crude cod liver oil.

Following the acclimatization period, the iliac and femoral arteriovenous fistulas were constructed in the positions as indicated in Figure 2. All of these arteriovenous fistulas were made in a side-to-side manner, under aseptic conditions, using a running stitch of fine silk (6-0) on an atraumatic needle. The lengths of all fistulas were measured at the conclusion of the anastomosis after release of the blood vessel clamps, and again at autopsy. The iliac arteriovenous fistulas were made immediately distal to the trifurcation of the abdominal aorta between the common iliac artery and vein. The femoral shunts were made two to four centimeters below the inguinal ligament between the femoral artery and vein. These femoral and iliac shunts were made large (See Tables II, III, IV). Earlier in our experiments the iliac and femoral arteriovenous fistula operations were staged a week or more apart. However, increasing experience has indicated that dogs tolerate without difficulty the construction of an iliac arteriovenous fistula in one leg and a femoral shunt in the other at the same operation.

The aorta-vena cava fistulas were constructed surgically in a similar side-to-side manner just proximal to the trifurcation of the abdominal aorta as indicated in Figure 3. In our experience the optimum size for the aorta-vena cava shunts has been from 8 to 15 mm. If these lengths are exceeded, an increasing number of the animals will promptly die of cardiac decompensation. This observation is in contrast to that made in the case of the iliac and the femoral arteriovenous shunts where the diameter of the constructed fistula in all cases substantially exceeded that of the parent vessels, so that minor differences in the length of these large fistulas appeared to be unimportant physiologically.

Our experience also has indicated that the longer the postoperative interval allowed for the compensatory changes of the arteriovenous shunts to take place, the more susceptible the animals have become to bacterial infection.

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*Vermiplex, Pitman-Moore Co., Div. Allied Laboratories Inc., Indianapolis, Ind.

**Virogen, Pitman-Moore Co., Div. Allied Laboratories Inc., Indianapolis, Ind.

***Lexone, E. I. duPont deNemours and Co., Inc., Wilmington, Delaware.

FIGURE 5

FIGURE 6

Figure 5, Dog 1345: Aortic Valve Bacterial Endocarditis.
Figure 6, Dog 1345: Iliac and Femoral Arteriovenous Fistulas.
Note: The iliac fistula is on the left.

All animals, except those of Group 3 with only a short recovery after their shunt operations before bacterial injections were begun, were given routinely prophylactic injections of penicillin-in-oil, 1,500,000 units daily, for varying periods of time up to a week after each operative procedure.

A more detailed description of some of the conditions pertaining to these experiments follows:

Group 1: Nineteen Dogs With Bilateral Arteriovenous Fistulas Receiving Intravenous *Injections of Beta Hemolytic Streptococcus.*

Eighteen of the 19 dogs in this group had an iliac arteriovenous fistula in one leg and a femoral arteriovenous shunt in the other leg. The remaining dog had bilateral iliac arteriovenous shunts.

The animals of this group have been divided into three subgroups upon the basis of the bacterial dose injected. Data upon the size of the fistulas and the recovery period allotted after fistula construction before bacterial injections were begun are listed in a detailed manner for each animal in subgroups 1A and 1B in Tables II and III respectively; and has been shown in a summarized form for the dogs of subgroup 1C in Table IV.

Group 2: Seven Dogs With Aorta-Vena Cava Arteriovenous Fistulas Receiving Bacterial Injections.

A detailed summary of the fistula size, the postoperative recovery interval, and the type and amount of the bacteria injected in the seven animals of this group is contained in Table V.

Group 3: Ten Dogs With One Femoral Arteriovenous Shunt Receiving Bacterial Injections.

Six of the ten dogs of this group had a single large arteriovenous shunt (24-25 mm. in length), and the other four had a single small shunt (10-11 cm. in length) between their femoral artery and vein.

In this group, the postoperative recovery period before bacterial injections were begun was intentionally varied from two to 116 days as indicated in Table VI in order to assay the relative importance of varying durations of a small increase in cardiovascular stress in localizing the pathological involvement to the heart valves and kidney glomeruli. Also, it was anticipated that when there was a very short interval between construction of the arteriovenous shunts and the intravenous injection of bacteria, the animals might acquire an infection at their fistula site, and the consequent continuous bacteremia plus a definite but small increase in cardiovascular stress (from the single femoral arteriovenous fistula) would provide a test of the relative importance of these two factors (i.e. size of shunt vs. continuous bacteremia) in localizing bacterial involvement to the valve leaflets and kidneys.

Group 4: Seventeen Normal Dogs Receiving Bacterial Injections.

These 17 control dogs were similar in all respects to those of Group 1, 2, and 3, except for the absence of arteriovenous fistulas. These normal dogs received intravenous injection in the amounts indicated in Table VII of one or the other of the two bacterial strains used in these experiments.

Results

Group 1A: Bilateral Lower Extremity Arteriovenous Fistulas. (0.005 ml. of bacterial broth).

Of the seven dogs in Group 1A with bilateral arteriovenous fistulas of the size and positions as indicated in Table II and Figure 2, three (Dogs Nos. 194, 196, 200) developed a persistent septicemia following intravenous

TABLE III: PRODUCTION OF ENDOCARDITIS IN DOGS WITH BILATERAL† ARTERIOVENOUS FISTULAS

Beta Hemolytic Streptococcus, 0.05 Ml. per Day††

Dog No.	Sex and Wt., Kg.	— — ARTERIOVENOUS FISTULAS — — Location	Length mm	Duration at Start of Bacterial Injections Days	INTRAVENOUS DOSE OF 24-HR. BROTH CULTURE Lancefield Group	Ml./Day	No. Days	Results	Survival After First Bacterial Injection, Days	Heart Valves Involved
745	F, 21.2	Iliac Femoral	22 23	25	A*	0.05	7	Died, Bacterial Endocarditis	29	Mitral, Aortic
123	M, 7.0	Iliac Femoral	18 13	25 22	D**	0.05	7	Sacrificed, Normal Heart and Kidneys	63	—
1523	M, 16.8	Iliac Femoral	24 21	43 43	D**	0.05	7	Sacrificed,§ Bacterial Endocarditis	14	Mitral
1345	M, 18.2	Iliac Femoral	29 23	44 37	D**	0.05	7	Died, Bacterial Endocarditis	42	Mitral, Aortic
1401	M, 17.0	Iliac Femoral	24 25	69 61	D**	0.05	7	Died, Bacterial Endocarditis	49	Mitral, Aortic
56	M, 15.1	Iliac Femoral	23 19	137 14	D**	0.05	7	Died, Bacterial Endocarditis	60	Aortic

*Type XIV of Beta Hemolytic Streptococcus (A) — Average colony count per milliliter of a 24-hr. broth culture = 60,000,000.

**Average colony count per milliliter of a 24hr. broth culture = 1,500,000,000 organisms.

†An Iliac Arteriovenous Fistula in one leg, and a femoral arteriovenous shunt in the other leg.

††Animals of sub-group 1B in text.

§At autopsy this dog had the incidental finding of a congenital heart defect (aneurysm of the interventricular septum).

No. of dogs with arteriovenous fistulas injected = 6

No. of dogs with endocarditis = 5

injections of only 0.005 ml. per day of a 24-hour broth culture of the "Strain I. F." beta hemolytic streptococcus for five to seven consecutive days. At autopsy all three of these dogs had vegetative endocarditis involving the mitral or aortic valves, and Dog 194 had in addition to the endocarditis an acute diffuse proliferative glomerulonephritis, Grade 1 plus. This dog was

TABLE IV: PRODUCTION OF ENDOCARDITIS IN DOGS WITH BILATERAL* ARTERIOVENOUS FISTULAS

Beta Hemolytic Streptococcus (Lancefield Group D), 0.5 Ml. per Day†

No. of Dogs	Interval From Last Fistula Until Bacterial Injections Started, Days▲	Intravenous Dose of 24-Hour Broth Culture♦	
		Ml./Day	No. Days
6	32 (14 to 56)	0.5	7

TABLE IV (Continued)

RESULTS			
No. Died	No. With Endocarditis	No. With Glomerulonephritis	Survival From First Bacterial Injection, Days▲
6 (100%)	6 (100%)	0	23 (12 to 37)

*An Iliac Arteriovenous Fistula in one leg, and a femoral arteriovenous shunt in the other leg.

▲Mean Value and Range.

♦Average Colony Count per Milliliter of 24-hour Broth Culture of this Strain = 1,500,000,000 Organisms.

† = Animals of Sub-group 1C in text.

FIGURE 7. *Dog 1393. Aortic Valve Endocarditis:* Produced by method illustrated in Figure 2 utilizing 0.5 ml. of a 24-hour broth culture of Beta Hemolytic Streptococcus injected intravenously once daily for seven days.

sacrificed when obviously in a moribund condition 26 days after the start of bacterial injections.

A brief mention of the methods of classifying the glomerulonephritis observed in these dogs is included in the section on pathology below. A more detailed pathological description together with a discussion of the pathogenesis of these renal lesions has been presented in a separate publication.[5]

The other two dogs with endocarditis (Nos. 200 and 196, Table II) died 31 and 59 days respectively from the time of their first bacterial injections. In this regard, it might be mentioned that once a dog with large arteriovenous fistulas develops a septicemia, death has been the invariable result. We have not observed any instances of spontaneous recovery.

Moreover, it is noteworthy in this group of seven animals who received a relatively small innoculation of bacteria and in which the incidence of endocarditis is just becoming apparent, that of the three dogs developing endocarditis, all had the longer intervals of recovery between the time of

TABLE V: PRODUCTION OF ENDOCARDITIS AND RESULTS OF BLOOD CULTURES IN DOGS WITH AORTA-VENA CAVA FISTULAS

Beta Hemolytic Streptococci†

		AORTA-VENA CAVA FISTULA		INTRAVENOUS DOSE OF BETA HEMOLYTIC STREPTOCOCCI (24-Hour Broth Culture)			
Dog No.	Sex and Wt., Kg.	Length, mm.	Duration at Start of Bacterial Injection Days	Lancefield Group	Ml./Day	No. Days	Dates of Bacterial Injections
221	M, 18.8	12	33	D*	0.005	7	(Inc.) 3/15-3/21
783	M, 16.7	10	26	A**	0.5	7	(Inc.) 7/18-7/24
420	F, 15.4	12	59	A**	0.5	7	(Inc.) 4/16-4/22
419	M, 19.3	14	69	A**	0.5	7	(Inc.) 4/16-4/22
740	F, 16.4	8	69	A**	0.5	7	(Inc.) 7/18-7/24
286	F, 18.3	15	76	A**	0.5	7	(Inc.) 4/16-4/22
614	M, 18.8	12	106	A**	0.5	7	(Inc.) 7/18-7/24

† = Animals of Group 2 in text.

*"Strain I.F." of Beta Hemolytic Streptococcus
(D) = Average colony count of a 24-hr. culture = 1,500,000,000 organisms per ml.

**Type XIV of Beta Hemolytic Streptococcus
(A) = Average colony count of a 24-hr. culture = 60,000,000 organisms per ml.

No. of dogs with aorta-vena cava fistulas injected = 7
No. of dogs with bacterial endocarditis = 6
No. of dogs with acute diffuse proliferative glomerulonephritis = 1

establishment of their arteriovenous fistula load and the injection of bacteria, and one of the three (Dog 194, Table II) had a larger arteriovenous fistula load (bilateral iliac shunts). These findings are in accord with our previous observations[2,3] that the increased susceptibility to infection is directly correlated with increased cardiovascular stress, and that the latter is dependent upon the diameter of the fistulous openings, the size of the parent vessels, and the duration of the shunts. In reference to the duration of a shunt, it has been well substantiated by Holman[4] that an arteriovenous shunt over a period of time is an ever steadily progressing parasite upon the cardiovascular system.

TABLE V (Continued)

	RESULTS OF BLOOD CULTURES				
Dog No.	Date	No. of Beta Streptococci /Ml. of Blood	RESULTS	Survival After First Bacterial Injection, Days	Heart Valves Involved
	3/14	Negative			
	3/21	Negative			
	3/26	11			
	3/30	17	Died, 4/8, Bacterial		
221	4/2	460	Endocarditis	24	Mitral
	7/9	Negative			
	8/2	1280			
	8/7	2400			
	8/14	>5000			
	8/21	>5000			Mitral
	8/28	>5000	Died, 9/5, Bacterial		Aortic
783	9/4	2080	Endocarditis	49	Pulmonary
	4/16	Negative			
	4/30	6			Mitral
	5/8	352	Died, 5/22, Bacterial		Aortic
420	5/15	789	Endocarditis	36	Pulmonary
	4/16	Negative			
	4/30	3			
	5/8	116			
	5/15	96			
	5/22	126	Died, 6/17, Bacterial		
	5/29	552	Endocarditis and		Mitral
	6/5	1250	Proliferative		Aortic
419	6/12	2680	Glomerulonephritis	62	Tricuspid
	7/9	Negative	Died, 8/18, Cardiac		
	7/30	Negative	Failure, Valvular and		
	8/7	Negative	Myocardial Fibrosis,		
740	8/14	Negative	Non-inflammatory	31	Mitral
	4/16	Negative			
	4/30	2	Died, 5/11, Bacterial		
286	5/8	75	Endocarditis	25	Mitral
	7/9	Negative			
	7/30	1			
	8/7	Negative			
	8/14	1			
	8/21	1 to 2			
	8/28	26			
	9/4	25	Died, 9/15, Bacterial		Mitral
614	9/11	300	Endocarditis	58	Aortic

Group 1B: Bilateral Lower Extremity Arteriovenous Fistulas. (0.05 ml. of bacterial broth).

Increasing the amount of the intravenous innoculum of the 24-hour broth culture to 0.05 ml. per day for seven consecutive days resulted in bacterial endocarditis in five of the six dogs with bilateral lower extremity arteriovenous fistulas (Table III). Again it should be noted that the only animal of this group not developing endocarditis (No. 123) was the only one of the animals with the shortest postoperative interval for the compensatory changes of shunts to take place in. One animal of this group (Dog 745, Table III) received 0.05 cc. of the Type XIV Beta Hemolytic Streptococcus (Lancefield Group A) instead of the "Strain I. F." Lancefield Group D organism. However, there was no essential difference in the character of the valvular pathology produced by this strain.

Figures 4 and 5 are from Dog 1345, representative of this group, and depict the extensive mitral and aortic valve endocarditis present at death 42 days after the initial injection of bacteria. Figure 6 shows the iliac and femoral arteriovenous fistulas from this same animal.

In the four dogs of group 1B, in which the endocarditis was allowed to terminate in death of the animal, the average duration of life from the initial injection of bacteria until death was 45 days.

FIGURE 8: Photomicrograph of Aortic Valve Bacterial Vegetations from Dog 1393. *Note:* The large colonies of bacteria (dark staining areas) in the platelet thrombus adherent to the valve leaflet, also the proliferative reaction within the leaflet.

TABLE VI: RESULTS OF BACTERIAL INJECTION INTO DOGS WITH A SINGLE FEMORAL ARTERIOVENOUS FISTULA†
Beta Hemolytic Streptococcus (Lancefield Group D)*

Results, All Dogs: Sacrificed, Negative Heart and Kidneys.

			ARTERIOVENOUS FISTULA		INTRAVENOUS DOSE OF 24-HR. BROTH CULTURE*	
Dog No.	Sex and Wt., Kg.	Location	Length, mm.	Duration At Start of Bacterial Injections, Days	Ml./Day	No. Days
120	M, 14.0	Femoral	10	4	0.5	7
1918	M, 12.7	Femoral	10	6	0.5	7
119	M, 13.4	Femoral	10	9	0.5	7
814	F, 20.5	Femoral	11	30	0.5	7
487	F, 17.9	Femoral	24	2	0.5	7
543	M, 18.7	Femoral	24	10	0.5	7
497	M, 17.6	Femoral	25	14	0.5	7
637	M, 13.9	Femoral	25	30	0.5	7
433**	M, 21.9	Femoral	25	50	0.5	7
1953	M, 16.4	Femoral	24	116	0.5	7

†Animals of Group 3 in text.
*Average colony count of a 24-hour broth culture of this strain. ("I.F.") = 1,500,000,000 organisms per ml.
**Dog was also castrated.

No. of dogs with single femoral A.V.F. injected = *10*
No. of dogs with endocarditis = *0*

TABLE VII
RESULTS OF BACTERIAL INJECTIONS INTO NORMAL DOGS†
Beta Hemolytic Streptococcus

Results, All Dogs: No Endocarditis, No Glomerulonephritis

		INTRAVENOUS DOSE OF BETA HEMOLYTIC STREPTOCOCCI (24-Hour Broth Culture)	
No. Dogs	Lancefield Group	Ml./Day	No. Days
5	D*	0.5	7 to 22
2	D*	2.0	7
5	D*	50.0	2 to 7
3	A**	5.0	7
2	A**	10.0	7

†Animals of Group 4 in text.
*"Strain I.F." of Beta Hemolytic Streptococcus (D) = Average colony count of a 24-hr. broth culture = 1,500,000,000 organisms/ml.
**Type XIV of Beta Hemolytic Streptococcus (A) = Average colony count of a 24-hr. broth culture = 60,000,000 organisms/ml.

No. of normal dogs injected = *17*
No. with endocarditis or glomerulonephritis = *0*

Group 1C: Bilateral Lower Extremity Arteriovenous Fistulas. (0.5 ml. of bacterial broth).

All of the six dogs of Group 1C (Table IV), with large bilateral arteriovenous fistulas of the size and positions portrayed in Figure 2, developed a persistent bacteremia and all died of endocarditis following the intravenous injection of 0.5 ml. of a 24-hour broth culture of the Beta Hemolytic Streptococcus† once a day for seven consecutive days. The average survival time for these six animals was 23 days from the beginning of their bacterial injections. The range of survival varied from 12 to 37 days in this group. None of the six dogs in this group developed glomerulonephritis. These results are summarized in Table IV. Figures 7 and 8 depict the aortic valve endocarditis in one of the dogs of this group dying 30 days after the first injection of bacteria. The majority of these dogs with endocarditis develop either or both systolic and diastolic cardiac murmurs.

In all of the dogs of Group 1 with bilateral arteriovenous fistulas receiving bacterial injections, frequent blood cultures were performed. This data, which has been previously presented elsewhere[3,5,8] in detail for some of these dogs, indicates that the bacteremia usually is well established by the conclusion of the five to seven day course of bacterial injections; and once established, the septicemia always becomes progressively more severe as manifested by a steadily rising bacterial count in the animal's blood, and terminates invariably in death of the dog.

†Strain I. F.

FIGURE 9. *Dog 783. Pulmonary Valve Endocarditis:* Produced by method depicted in Figure 3 utilizing 0.5 ml. of a 24-hour of beta hemolytic streptococcus culture injected intravenously once daily for seven days in a dog with a single aorta-vena cava shunt. *Note:* Involvement of the pulmonary valve is the least frequent of the four valves.

Group 2: Aorta-Vena Cava Fistulas.

In this group there were seven animals studied with a single aorta-vena cava fistula made at the lower end of the abdominal aorta as shown in Figure 3. One of these dogs (No. 221, Table V) was given a series of seven consecutive daily injections of 0.005 ml. each of "Strain I. F."†† This dog developed and succumbed to bacterial endocarditis 24 days later. The remaining six dogs in this group were given a daily intravenous injection of 0.5 ml. of the Type XIV, Beta Hemolytic Streptococcus (Lancefield Group A) for seven consecutive days. All of these six animals died, and five had severe valvular destruction due to bacterial vegetations (Figure 9, Dog 783). One dog (No. 419) also had an acute diffuse proliferative glomerulonephritis, grade 3 plus. The sixth animal (Dog 740) although classified as negative, at autopsy had grossly a very definite row of rheumatic-like nodules along the edge of the mitral leaflets. Microscopically, examination of these leaflets showed a severe fibrosis. There was also a widespread severe fibrosis of the myocardium. A final interpretation of the significance of these findings in this dog has not been made.

The average duration of life for the six dogs of this group dying of bacterial endocarditis was 42 days from the first injection of bacteria.

A detailed analysis of the blood culture data for all of the dogs of this group has been included in Table V. The dogs developing endocarditis show a progressive septicemia similar to that observed in Group 1 animals.

††Lancefield Group D, Beta Hemolytic Streptococcus.

TABLE VIII: RELATIONSHIP OF CARDIOVASCULAR STRESS AND INCREASED SUSCEPTIBILITY TO BACTERIAL INFECTION

SUMMARY

Amount of Cardiovascular Stress	No. Dogs	Total▲ Intravenous Bacteria Dose (24-Hr. Broth Culture) Milliliters	No. With Endocarditis	No. With Diffuse Proliferative Glomerulonephritis
Bilateral A.V.F. (Lower Extremities)	7	0.025 to .035*	3 (43%)	1 (14%)
Bilateral A.V.F. (Lower Extremities)	6	0.35*	5 (84%)	1 (17%)
Bilateral A.V.F. (Lower Extremities)	6	3.5*	6 (100%)	0
Aorta-Vena Cava	7	.035* to 3.5**	6 (86%)	1 (14%)
Single Femoral A.V.F.	10	3.5*	0	0
None (Normal Dogs)	17	3.5 to 350.0* 35.0 to 70.0**	0	0

▲Total Dose = Daily dose (in milliliters) of a 24-hour broth culture multiplied by number of days injected.

*Beta Hemolytic Streptococcus ("Strain I.F.", Lancefield Group D).

**Beta Hemolytic Streptococcus (Type XIV, Lancefield Group A).

Group 3: Single Femoral Arteriovenous Shunt.

In the 10 dogs with a single femoral arteriovenous fistula, the daily intravenous injection of 0.5 ml. of a 24-hour broth culture of beta hemolytic streptococcus (Group D, "Strain I. F.") for seven consecutive days did not cause endocarditis, glomerulonephritis, nor were there any other apparent ill effects. The results in this group of animals are summarized in Table VI. This zero incidence of endocarditis is in direct contrast to the 100 per cent incidence of endocarditis that was observed in the dogs with larger increases in cardiovascular stress (bilateral arteriovenous fistulas) receiving injections of the same magnitude of the same bacterial strain (Group 1C). It should also be noted that, as anticipated, in the six dogs receiving bacterial injections when their femoral fistulas were from two days up to 31 days duration, it is quite likely that the fistula became the site of a temporary localized infection. This conclusion is based upon the fact that in these six animals the blood culture studies indicated a significant bacteremia (up to 419 colonies per ml. of blood). Nevertheless, even in the presence of this temporary bacteremia, there was no tendency in these animals with a single femoral fistula for the bacterial infection to involve the endothelium of the kidneys or the heart, and the blood cultures gradually became sterile again in all animals without treatment. Space does not permit a detailed presentation of this blood culture data here, but a detailed analysis of the results of the blood cultures in four of the animals of this group has also been presented elsewhere.[5]

Group 4: Normal (Control) Animals.

The results (Table VII) of the injection of these same bacterial strains into 17 normal dogs (Group 4) are also in distinct contrast to the results observed in dogs with bilateral arteriovenous shunts. In these normal dogs, the intravenous injections as indicated in Table VII of the two strains of bacteria used in these experiments caused no endocarditis nor glomerulonephritis and surprisingly few ill effects. The transient occurrence of fever was observed, and one of the dogs receiving 50 ml. per day of the broth culture of "Strain I. F." died in a shock-like state after the second daily intravenous injection of 50 ml. All other animals of this group remained in excellent health, and it was necessary to sacrifice them for autopsy.

Blood culture studies have been performed in these normal dogs receiving intravenous injections of bacteria and have indicated[5] that a very low grade bacteremia (one to two colonies of bacteria per ml. of blood) existed for 24 to 72 hours immediately following the cessation of a course of bacterial injections. After that time, the blood again became sterile.

It should be noted that the total numbers of beta hemolytic streptococci (Group D, Strain I. F.) organisms injected into these normal control animals (50 ml. per day for seven days), were as much as *14,000 times* greater than the minimum number of organisms (0.005 ml. per day for five days) necessary to produce endocarditis in the dogs with large bilateral arteriovenous fistulas. Likewise, in the case of the Lancefield Group A Strain of beta

hemolytic streptococcus, the numbers of bacteria injected without ill effects into the normal dogs were *20 times* greater than that which produced endocarditis regularly in the dogs with aorta-vena cava fistulas. These comparisons of the pronounced differences in results between the injection of bacteria into normal dogs and those with large arteriovenous fistulas provide striking evidence of the importance of the physiological alterations associated with large arteriovenous fistulas in promoting endothelial susceptibility to infection.

Pathology

In the dogs dying of endocarditis produced by these methods, the gross and microscopic pathology has been described to some extent in previous publications.[1-3,5] A full and detailed report on the microscopic pathology in these dogs and others is in preparation. Briefly, it may be stated that grossly and microscopically, the valvular vegetations are of two distinct types, bacterial-like and rheumatic-like. The bacterial-like lesions predominate in these animals (Figure 8) with scattered smaller lesions resembling rheumatic endocarditis (fibrinoid formation, proliferation, mononuclear infiltrate, and absence of bacteria) seen both in association with the bacterial lesions and less commonly being found as the only type of lesion. Mycodarditis and, as has been indicated, diffuse proliferative glomerulonephritis are associated with the endocarditis in some animals. However, typical Aschoff nodules have not been observed in the myocardium of any of these animals to date.*

The glomerular lesions occurring in these animals have been graded** 1 plus to 3 plus on the basis of criteria previously described.[5] In this regard, it is emphasized that in several dogs classified as having negative kidneys there was seen a definite endothelial cell proliferation present in some glomeruli, but the majority of the glomeruli were not involved. It is considered quite likely that these animals with lesser degrees of involvement represent an early stage of the same pathologic process.

Discussion

By utilizing the cardiovascular stress of bilateral lower extremity or a single aorta-vena cava fistula together with the transient bacteremia produced by the daily intravenous injections of from 0.005 to 0.5 ml. of a 24-hour broth culture of beta hemolytic streptococci (Lancefield Group A or D Strains) for five to seven consecutive days, bacterial endocarditis has been produced in from 33 per cent to 100 per cent of the dogs depending upon the number of bacteria introduced, the size of the arteriovenous fistula load, and the duration† of the arteriovenous fistulas at the time of

*We are indebted to Professor B. J. Clawson, Department of Pathology, University of Minnesota, who has examined and classified all of the microscopic sections from these animals.

**We are indebted to Professor E. T. Bell, Department of Pathology, University of Minnesota Medical School, who has examined and graded all of the renal pathology observed in these animals.

†Susceptibility to bacterial infection increases with the duration.

injection of bacterial organisms. Once established, this endocarditis leads uniformly to the death of the animal. These findings constitute a further confirmation of our initial observation[1,2] indicating that dogs with large arteriovenous fistula loads are unusually susceptible to bacterial involvement of their heart valves and kidney glomeruli.

In normal dogs, the intravenous injection of numbers of the same bacteria up to *14,000 times* as great as the minimum numbers necessary to produce endocarditis in the animals with large arteriovenous shunts, did not cause endocarditis nor glomerulonephritis. And further, in normal dogs the intravenous injection of numbers of bacteria *100 times* the amount necessary to produce endocarditis in 100 per cent of the animals with arteriovenous shunts, did not cause endocarditis nor glomerulonephritis.

The difficulties of attempting to produce endocarditis or glomerulonephritis by bacterial injection alone in normal animals, particularly the dog, has been previously documented by a number of investigators. Kinsella and Muether[6] were unable to produce endocarditis in dogs by injecting streptococci. Dick and Schwartz[7] were able to produce endocarditis in approximately 30 per cent of 83 dogs only by continually injecting doses of up to 100 cc. of broth cultures of streptococci intravenously four times weekly for varying periods up to six and three-quarter years. Likewise, we have recently reviewed[5] briefly in another publication the difficulties recorded by earlier investigators in attempting experimentally to produce diffuse proliferative glomerulonephritis by injection of bacteria or their toxins.

The findings in these experiments, which are summarized in Table VIII, provide an unequivocal demonstration of the effects of a systemic cardiovascular stress in the form of large arteriovenous fistulas in prompting infection of the heart valves and the kidney endothelium. However, the precise mechanisms involved need further identification.

Appreciation of this concept of the relationship of increased cardiovascular work and increased susceptibility to bacterial infection has had several dividends of practical and theoretical significance.

First, of immediate practical interest has been the development of a new and effective experimental method for the reproduction and study, in a readily available laboratory animal, of two clinically important diseases, i.e., endocarditis and proliferative glomerulonephritis.

Further, in another series of dogs, we have utilized this experimental method for the production of chronically scarred heart valves,[8] very similar to those seen clinically, by allowing the vegetations to become well established upon the heart valves and then instituting intensive therapy to sterilize the blood stream. However, in this regard, the relative ineffectiveness of penicillin and the other antibiotics aureomycin and streptomycin in the treatment of this endocarditis and glomerulonephritis is noteworthy. There appears to be a close similarity in this feature to certain cases of human endocarditis particularly those associated with strains of bacteria less susceptible to the antibiotics. In our experiments reported recently,[8] 80 per cent of the dogs, with endocarditis established by the method described herein and then treated intensively with antibiotics,

died of progressive valvular lesions even in spite of surgical excision of the arteriovenous fistulas in one animal. Likewise, there was suggested evidence that dogs whose endocarditis was treated with antibiotics had a higher incidence of glomerulonephritis. This latter observation may be related to the fact that the treated animals survived longer with a septicemia before eventually dying. Further study of this important consideration is necessary. Particularly is this true, inasmuch as the intimate mechanism by which bacteremia produces glomerulonephritis in these animals is not clearly understood at present.

It is perhaps readily apparent that the observations herein reported may also contribute to an elucidation of the mechanism of production of bacterial endocarditis observed in clinical patients secondary to acquired valvular heart disease and secondary to congenital heart disease. Some speculations in these regards have been offered previously.[3,8]

Finally, appreciation of this concept of stress and infection based upon the present experimental observations would appear to offer a unique opportunity to ascertain possible fundamental factors affecting susceptibility and resistance to bacterial infections in general.

Data derived from physiologic studies of the effects of arteriovenous fistulas upon cardiovascular function in these dogs[9] have suggested that the susceptibility to endocarditis observed is related to two main factors:

1) A mechanical factor pertinent to the enormous increase in the work thrust upon these hearts by the large arteriovenous fistulas. Traumatic damage to the heart valves is included within this heading.

2) An endocrine factor due possibly to an imbalance or altered hormone secretion from the adrenal glands.

It seems likely that these mechanical factors set in motion certain secondary physiological reactions such as the adrenal hypertrophy which has been reported.[1,2] These secondary physiological reactions then determine the end result. Obviously, it may be of considerable clinical importance to experimentally define more precisely the changes associated with the increased cardiovascular work that are responsible for this altered susceptibility to infection. Identification of one of these mechanisms which appears to be significant in this regard has been the recent finding[10] that bilateral total adrenalectomy,* which was without effect upon the occurrence of septicemia in these dogs with large arteriovenous fistulas, *completely protected* the heart valves in these same animals with a continuous septicemia against invasion by bacteria and the formation of vegetations.

The clarification of such mechanisms as this, could forecast the development of more effective methods of prophylaxsis and therapy for endocarditis, glomerulonephritis, and perhaps for bacterial infections in general.

SUMMARY AND CONCLUSIONS

1) By combining the effects of systemic cardiovascular stress produced by large arteriovenous fistula loads with bacteremia, a new method has

*The adrenalectomized dogs were maintained on sodium chloride and desoxycorticosterone acetate.

been described for the experimental production of endocarditis and acute diffuse proliferative glomerulonephritis in dogs.

2) Bilateral lower extremity (iliac and femoral), or single aorta-vena cava fistulas are effective for use in this experimental method.

3) Seventeen unoperated normal dogs were given injections of bacterial organisms in numbers up to 14,000 times the numbers of bacteria of the same species and strains as were followed by heart valve or kidney lesions in the dogs with large arteriovenous fistula loads. There was in no instance the occurrence of either endocarditis nor glomerulonephritis in these normal dogs.

4) Likewise, in 10 dogs with single femoral arteriovenous anastomoses receiving intravenous injections of bacteria in comparable numbers, neither endocarditis nor glomerulonephritis occurred.

5) Because of the absence of lesions in the unoperated normal dogs and dogs with single femoral arteriovenous shunts given the same bacteria in the same or much larger numbers than given to the animals with large fistulas subsequently showing valvular or renal lesions, it is concluded that the increased work of the heart plays a major role in determining the susceptibility of these animals to endocarditis and glomerulonephritis.

6) The pathogenesis of these experimental observations depends upon the fact that increasing the work of the heart by means of large arteriovenous fistula loads create or set in motion certain mechanical and, or endocrine alterations which in turn produce a specific and significant increase *(up to 14,000 times)* in the susceptibility of the endothelial surfaces of the heart and kidneys to bacterial infection. The factual data supporting these conclusions are presented.

7) By utilizing these experimental methods, it may be possible to identify more precisely the physiological alterations which occur in response to increased cardiovascular work and which are apparently responsible for this great increase in susceptibility to bacterial infection observed in these studies. Such accomplishments, might forecast the development of more effective methods of prophylaxis and therapy for endocarditis, glomerulonephritis, and possibly for bacterial infections in general.

RESUMEN

1) Combinando los efectos de una sobrecarga cardiovascular general producida por una gran fistula arteriovenosa, con bacteriemia, se ha descrito un nuevo metodo para la producción experimental de endocarditis y glomerulonefritis aguda, difusa y proliferativa en los perros.

2) Las fistulas bilaterales de la extremidad inferior (iliac y femoral) o la fistula simple aorta-cava son efectivas para este método.

3) En diecisiete perros normales no operados se inyectaron bacterias en números hasta 14,000 veces los números de bacterias de las mismas especies y cepas de las que se usaron cuando fueron seguidas de lesiones del corazón en sus valvulas o lesiones de riñones en perros con grandes cargas sanguíneas después de fistulas arteriovenosas. No hubo un solo caso de endocarditis en los perros normales ni tampoco glomerulonefritis en esos mismos.

4) Igualmente, en diez perros con anastomosis simple femoral arteriovenosa que recibieron inyecciones intravenosas de bacterias en número comparable, no ocurrió endocarditis ni glomerulonefritis.

5) A causa de la ausencia de lesiones en el perro no operado y en los perros con simples intercomunicaciones arteriovenosas femorales, que recibieron las mismas cantidades de bacterias o mucho mas grandes que en aquellos perros con grandes fístulas que después mostraron lesiones renales o valvulares, se concluye que el aumento del trabajo del corazón desempeña un papel principal en la determinación de la susceptibilidad de estos animales a la endocarditis y a la glomerulonefritis.

6) La patogenia de estas observaciones experimentales se basa en el hecho de que con el aumento del trabajo del corazón por medio de grandes fístulas arteriovenosas, las sobrecargas producen cambios mecánicos o los provocan y a su vez accarrean alteraciones endócrinas que conducen a un aumento específico de la susceptibilidad (hasta 14,000 veces mas) de las superficies endoteliales del corazón y del riñón a la infección bacteriana. Los hechos que sostienen estas conclusiones son aquí presentados.

7) Utilizando estos datos experimentales puede ser posible identificar con precisión mayor las alteraciones fisiológicas que ocurren en respuesta al aumento del trabajo cardiovascular y que aparentemente son responsables de este gran aumento de la susceptibilidad observada en estos estudios. Tales realizaciones podrían llevar al desarrollo de métodos mas efectivos de profilaxis y tratamiento de las endocarditis, las glomerulonefritis, y posiblemente de las infecciones bacterianas en general.

RESUME

1) Les auteurs décrivent une nouvelle technique expérimentale pour provoquer chez le chien une endocardite et une glomérulonéphrite proliférative aigue. Ils utilisent à cet effet l'atteinte du système cardio-vasculaire, provoquée par une large fistule artério-veineuse renforcée par une bactériéme.

2) Pour cette méthode, sont valables les fistules bilatérales des extrémités inférieures (iliaque et fémorale) ou l'unique fistule aorte-veine cave.

3) Pour les chiens chez lesquels avaient été réalisées de grandes fistules artério-veineuses, les lésions atteignirent les valvules cardiaques et les reins. Chez 17 chiens normaux et non opérés on administra des bactéries de la même espèce et de la même souche que celles qui avaient été utilisées chez les chiens à fistules, mais jusqu'à 14,000 fois plus abondantes en quantité. Il n'y eut jamais ni endocardite ni glomérulo-néphrite chez ces chiens normaux.

4) De même, chez 10 chiens porteurs de simples anastomoses fémorales artério-veineuses ayant reçu des injections intraveineuses de la même quantité de bactéries, il n'y eut ni endocardite ni glomérulo-néphrite.

5) Il n'y eut pas de lésions chez les chiens normaux non opérés et chez les chiens atteints d'une simple fistule, alors que les chiens atteints de larges fistules furent atteints ultérieurement de lésions valvulaires ou rénales. Cela signifie que l'augmentation du travail cardiaque joue un rôle

majeur dans la susceptibilité de ces animaux à l'endocardite ou à la glomérulo-néphrite.

6) L'accroissement du travail du coeur par l'intermédiaire d'une large fistule artério-veineuse détermine donc des troubles mécaniques ou des altérations endocriniennes, qui sont responsables d'un accroissement spécifique de la susceptibilité à l'infection bactérienne des surfaces endothéliales du coeur et des reins.

7) Ces méthodes expérimentales ont rendu possible l'indentification plus précise des altérations physiologiques que sont consécutives à l'accroissement du travail cardio-vasculaire et qui sont, semble-t-il, responsables de l'augmentation considérable de la susceptibilité aux infections bactériennes. Ces travaux peuvent être l'origine de techniques plus efficaces dans la prophylaxie et le traitement des endocardites, des glomérulo-néphrites et peut-être même des infections bactériennes dans leur ensemble.

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Angulation Roentgenograms in Obscure Lung Lesions: A Standardized Technique

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Postero-anterior films of the chest frequently fail to reveal satisfactory evidence of the pathology which may be present. To obtain a better perspective of the lung lesions, it is often necessary to resort to lordotic and oblique films. The value of such positional roentgenograms, however, has been limited because the importance of definite methods of standardizing these films has not received sufficient consideration.

Sherman W. Atwell[1] recently stressed the importance of standardized oblique roentgenography of the chest, and observed that properly positioned oblique films can "open" obscure areas of the hilum, apex, and other parts of the lung. He has described an apparatus for standardizing films in the oblique projection.

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FIGURE 1: Lordotic positioning apparatus attached to cassette holder with patient in correct position.

The value of the lordotic position in the clarification of obscure lung lesions is well recognized. Clinicians, however, do not avail themselves sufficiently of this projection, possibly because of the fact that text-books have not stressed its importance and because no generally accepted technique has been described. The exact angulation of the lordotic position when a chest film is taken seldom receives proper consideration, and consequently it is difficult to duplicate accurately a lordotic film at a subsequent examination. Moreover, no mechanism is in general use which enables the radiologist to determine definitely, for comparative purposes, the degree of angulation of the lordotic position of the patient. We have found that a variation of five degrees in the lordotic positioning of a patient may make an important difference in the pathology observed on the film. The detection of the presence of a lung cavity may depend on this small degree of angulation.

Difficulties may also be met within chest films taken in the oblique

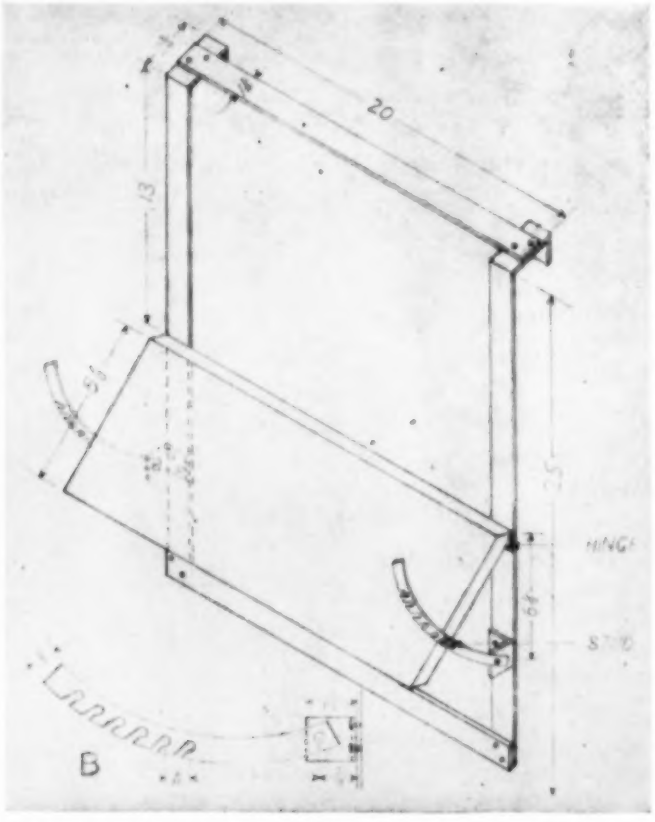

FIGURE 2: Detailed diagram of lordotic positioning apparatus; B, denotes details of metallic arc.

position. Here again there is no general acceptance of a standardized technique for duplicating the x-ray film, or of measuring the degree of angulation of the patient.

We have devised a mechanism for each of these positions which will permit the exact determination of the degree of angulation in the lordotic as well as oblique x-ray film of the chest.

The lordotic positioning apparatus consists of a metallic frame which can be easily attached to the cassette holder by means of metallic hooks or other attaching means at its upper end (Figure 1). The manner of attaching the apparatus will vary to conform with the different x-ray units. A board is hinged to the metallic frame and adjusted, by means of a stud, to a metal arc which is notched at 5 degree intervals to give the exact angulation. This metal arc has a radius or six and one-half inches and permits lordotic angulation from 30 to 55 degrees. Figure 2 presents a diagram of the lordotic positioning apparatus and gives its exact measurements.

In positioning the patient for a lordotic film the back rests against the angled board and the cassette holder, the elbows are directed anteriorly to bring the scapulae away from the lung fields, as will be noted in Figure 1.

In taking such a film the cassette is placed at the same height as for a postero-anterior chest roentgenogram; however, the tube is lowered seven inches and angled upward 10 degrees. Other technical factors include,

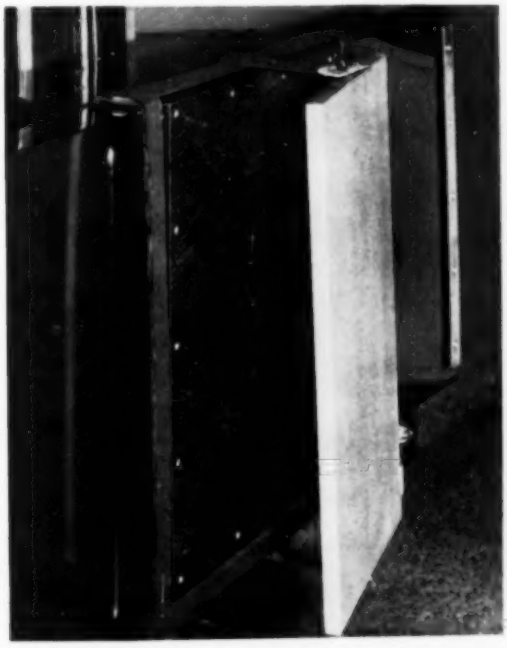

FIGURE 3: Oblique positioning apparatus attached to cassette holder.

focal-film distance of 48 inches, 10 milliampere-seconds, and the KVP is increased 4 kilovolts above that used in the PA view for that patient. The average angulation used is 45 degrees; however, a thin thorax is best positioned at 55 degrees, a deep chest at 30 or 35 degrees.

The oblique positioning apparatus consists of a similar frame with the Board attached at the center of its vertical axis. The degree of angulation is measured by a protractor which is fixed to the upper end of the apparatus (Figure 3). This apparatus is so constructed that it can also be attached to the fluoroscopic carriage (Figure 4). After the desired position is obtained fluoroscopically and the angulation definitely noted, the apparatus is then placed on the cassette holder and an x-ray film of the patient is taken in the same position as determined during fluoroscopy. Figure 5 gives a detailed diagram of the apparatus which is designed to be used on both the fluoroscopic carriage and cassette holder.

In taking such a film the technique is similar to that for a postero-anterior film; however, the KVP is increased 8 kilovolts to compensate for the obliquity of the patient and the added distance between the patient and the cassette.

A number of films are presented which demonstrate the possibilities of lordotic and oblique roentgenograms with variable predetermined degrees of angulation (Figures 6, 7 and 8).

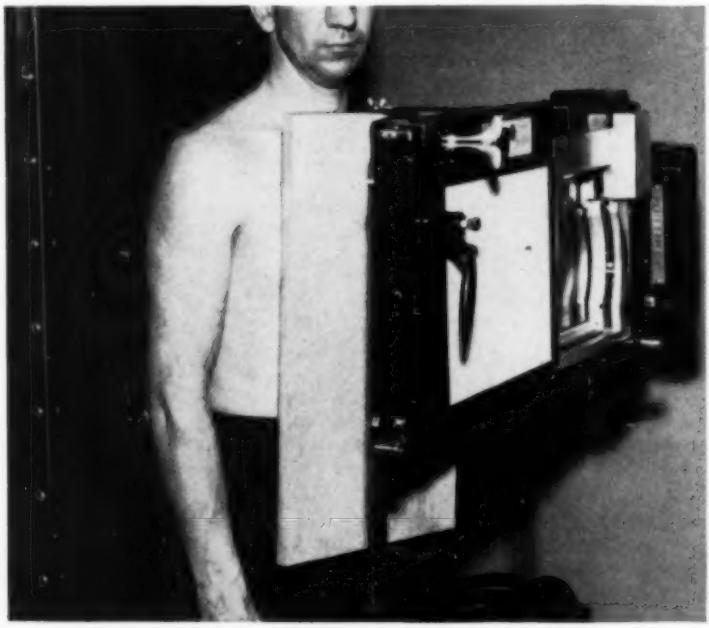

FIGURE 4: Oblique positioning apparatus attached to fluoroscopic carriage with patient in position.

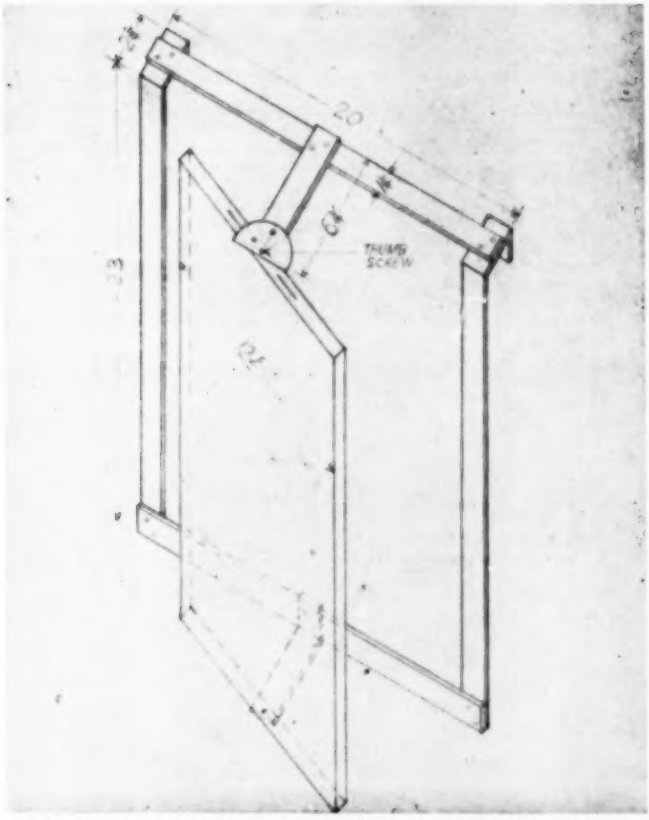

FIGURE 5: Detailed diagram of oblique positioning apparatus.

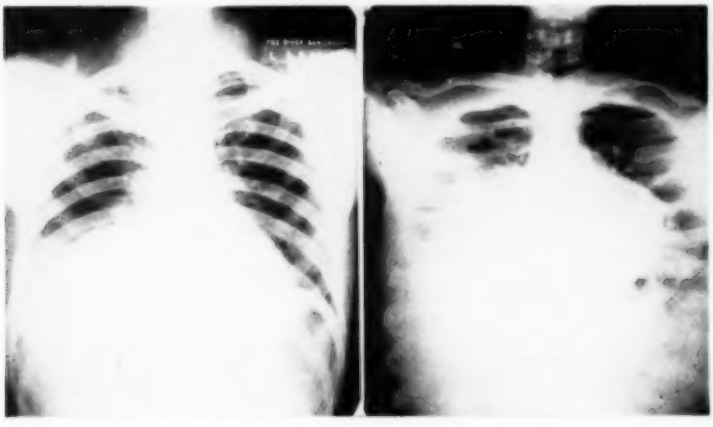

FIGURE 6: Arrow points to cavity in lordotic roentgenogram not visible in PA view.

SUMMARY

The diagnostic limitations of postero-anterior films of the chest and the value of standardizing lordotic and oblique projections are discussed.

A relatively simple method for obtaining predetermined angulation roentgenograms is presented.

Types of angulation apparatus are described for both lordotic and oblique films.

The possibilities of this method of chest roentgenography in obscure chest lesions is demonstrated.

Tomographic films frequently clarify chest lesions, but the required equipment is expensive and often not available. Moreover, the procedure

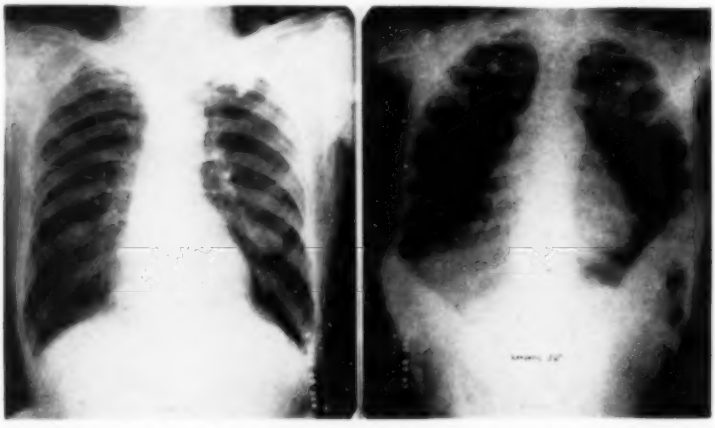

FIGURE 7: Arrow points to cavity in lordotic view, not evident in PA film.

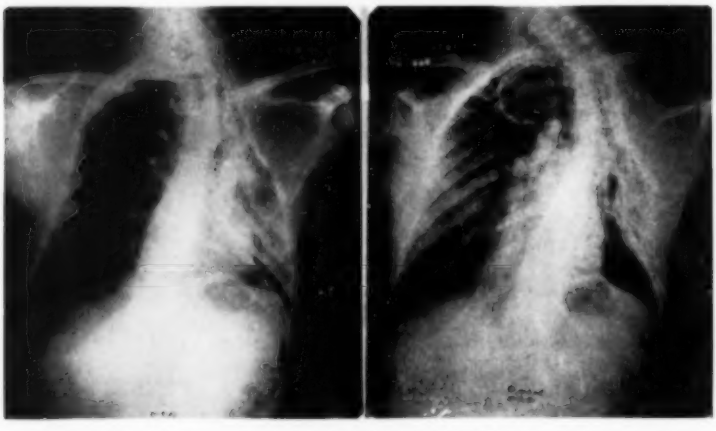

FIGURE 8: Giant cavity clearly outlined in oblique roentgenogram as compared to PA view.

is quite intricate and takes a good deal of time. Angulation films will in many instances eliminate the necessity for tomograms.

RESUMEN

Se discuten las limitaciones de las radiografías en postero-anterior y el valor de la estandarización de las proyecciones lordótica y en oblicua.

Un método relativamente sencillo para obtener una angulación predeterminada en las roentgenografías se presenta.

Se describen los tipos de aparatos de angulación tanto para la posición en lordosis como en oblicua.

Se demuestran las posibilidades de este método de radiografía del torax en las lesiones obscuras.

Las películas tomográficas frecuentemente aclaran estas lesiones del torax pero el equipo requerido es costoso y a menudo no se obtiene. Mas aún, le procedimiento es complicado y requiere mucho tiempo. Las peliculas en angulación en muchos casos eliminan la necesidad de tomogramas.

RESUME

Les auteurs discutent les limites de la valeur diagnostique des radiographies thoraciques en position antéro-postérieure et la valeur des positions en lordose, et en oblique.

Ils présentent une méthode relativement simple pour obtenir des radiographies selon différentes positions.

Ils donnent la description des techniques pour les positions en lordose et en oblique.

Les possibilités de cette méthode de radiographies pulmonaires dans les cas où les lésions ne sont pas nettes sont ainsi démontrées.

Fréquemment les tomographies permettent de préciser les lésions thoraciques, mais elles nécessitent un équipement cher et souvent impossible à se procurer. En outre, la technique en est souvent très compliquée, et prend beaucoup de temps. Les radiographies en différentes positions, dans bien des cas, permettent qu'on se passe de tomographies.

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The Genesis of Good Teaching

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The rumor is abroad that good teachers are born not made. While the phenomenon of congenital tagging of a teacher may occasionally occur, an analysis of the evidence suggests strongly that the same factors which make a good banker, a good tailor, a good artist, a good bookmaker, operate in the world of pedagogy. These factors are interest and hard work.

The physician occupies a curious place in this educational system. By long years of training in the general and special fields of medicine he has become eminently qualified to investigate the nature of human illness and to direct both absurdly simple and alarmingly complex therapeutic programs whose aim is the restoration of health. The Hippocratic Oath, to which he subscribes, imposes upon him the additional responsibility "to teach this art." Thus a quirk of professional mores has succeeded in equating training for care of the sick with training for teaching the care of the sick. It requires no great perspicacity to recognize that while the two are inseparable they are not necessarily equal.

Good teaching is a work of art and like any such work is meaningful only as it is colored by the artist. This being so, it is almost inevitable that a good teacher will develop certain methods, mannerisms, and technics that are uniquely his, which in another might be fatuous or offensive. The very nature of this experience makes it presumptuous for anyone to draw up a list and say *this* is what makes a good teacher. At the same time there is a recurrent *leitmotif* which runs through excellence in instruction everywhere, and it is the components of this theme that might be recalled even at the risk of boring by simplicity.

I *Preparation:*

There are few things more difficult for the clinical teacher to realize than that the mere fact of continuous contact with the problem of tuberculosis, for example, is not adequate for a lecture, seminar, or a conference, on even the most elementary phase of the subject. Familiarity with subject matter is only the beginning of preparation and is in many ways the least trying. Of equal importance is the time devoted to a consideration of the method and sequence of presentation, the illustrations to be cited, personal experiences recounted, visual aids employed, and the synthesis of all these parts into a vigorous and meaningful whole. Lest emphasis upon preparation be misinterpreted it should be pointed out that meaning can seldom, vigor never be transmitted from the teacher who reads to the student who writes.

While these matters might seem to apply most properly to the lecture

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method, they are of equal importance in less formal teaching exercises. The conference must have direction and pace, the seminar organization and design. It is only the ward round which the physician-teacher must face cold and alone, where ingenuity and experience must be relied upon to replace the more dependable method of thoughtful preparation.

It is a rule of thumb among educators, that for every teaching hour, two hours must be spent in preparation. It is an old rule and a good rule and it deserves the respectful consideration of any physician who calls himself a teacher.

II *Technics:*

Success in teaching depends ultimately upon the ability of the teacher to communicate with his students. In the absence of this rapport he is indulging at best in soliloquy and at worst in monologue. It is alarming to realize the number of teaching exercises which fall into one of these categories and how often the teacher fails to recognize his plight.

As teachers we usually think of this communication in terms of imparting information to students. It is worth noting that Webster lists an additional meaning: The interchange of ideas or opinions. Communication in this light becomes a dynamic state in which the student is an active participant rather than passive observer; and it is this kind of communication which pays the largest dividends in learning. Any technic which fails to provide an opportunity for the student to talk back will seldom achieve its greatest potential success. But such opportunity will flower only in a special environment which results directly from the teacher's

III *Attitudes:*

One of the greatest barriers to comfortable teacher-student relationships is the fact that the teacher probably knows more about the subject than the student and that the student, like any other of our breed, suffers acutely if his inferior position becomes too evident. Thus participation, which may reveal ignorance, is extremely difficult for students who want to appear at their best before an instructor and their fellows. This fact of human nature cannot be changed but the successful teacher manages to circumvent it. He accomplishes this by painstaking cultivation of two special qualities: patience and understanding.

These qualities should not imply that he will tolerate error, superficiality, or ignorance but rather that he will deal with these failures by logic and reason rather than emotion and appeal to authority. The instructor who bolsters his own ego by dismissing a student question as stupid needs a psychiatrist, not a teaching assignment. The teacher who jokes publicly at student failure has lost his effectiveness as well as his stature. The preceptor who demands conformance will succeed in turning out parrots, not scholars. Medical students are intelligent, quick, reasonably well balanced adults. To treat them as willful, somewhat retarded, exasperating children impedes both teaching and learning.

IV *Miscellany:*

There are a vast number of seemingly insignificant factors which often contribute to success in instruction. Three might be mentioned in passing.

Promptness is a much neglected quality in medical practice as any patient would willingly testify. Keeping one patient waiting is inconsiderate enough but keeping one hundred students waiting, or making them late for their next appointment by running over assigned time, is inexcusable.

Friendliness is helpful in any interpersonal relationship and it is particularly effective in breaking the barrier between student and faculty. If it is at all possible, students should be known and recognized by name.

Humor is a delight when used effectively and may accomplish what solemnity will not. But there are few things more dismal than humor which is inappropriate or fails to take fire.

V *Motivation:*

Left until last is the subject which requires the most delicacy by the writer and the most self examination by the reader.

It is unfortunately true that in many teaching institutions participation in the teaching program is a pre-requisite to professional advancement. It is also true that there are many highly qualified physicians whose interest in teaching is negligible. If these men are forced into a position of teaching or stagnating they will choose the former. But it would be unrealistic to expect brillance, or even competence from their performance. Teaching is too demanding a task to be assumed casually or irresponsibly. If it suffers because of this, then the blame must fall on administrators. This is a problem that requires the most careful consideration. Re-examination of local ground rules in the light of the requirements for successful teaching, the time and pain necessary for its accomplishment, might result in significant improvement.

These paragraphs have stressed certain general qualities which contribute to good teaching in any field. It would be impertinent to spell out a program for any specific subject, school, or department. These are individual matters. But any specific program which neglects such fundamental concepts may easily fail in the accomplishment of its goal.

For concrete suggestions let the teacher look back into his own past as a student who experienced both frustration and stimulation at the hands of teachers who were for some reason bad or good. Such experience culled and winnowed, might provide a substantial foundation upon which to build.

Report of the Committee on Physiologic Therapy

Presented at the Annual Meeting of the American College of Chest Physicians, June 5, 1952

The varieties of Intermittent Pressure Breathing were discussed at the meeting of the Committee on Physiologic Therapy. The views of three members of the Committee are summarized in the following reports:

Clinical use of intermittent positive pressure breathing combined with nebulization in pulmonary diseases, by Peter Theodos.

Respiratory acidosis including the use of intermittent pressure breathing, by M. S. Segal.

Intermittent positive pressure breathing with swift velocity expiration, i.e., exsufflation, intermittent negative pressure breathing and viscero-diaphragmatic breathing, by Alvan L. Barach, Chairman. Committee members were Maurice S. Segal, Albert H. Andrews, George R. Meneely, Charles E. Lyght, Peter A. Theodos and George W. Wright.

INTERMITTENT POSITIVE PRESSURE BREATHING WITH SWIFT VELOCITY EXPIRATION, i.e., EXSUFFLATION, INTERMITTENT NEGATIVE PRESSURE BREATHING, AND VISCERO-DIAPHRAGMATIC BREATHING

ALVAN L. BARACH, M.D., F.C.C.P.
New York, New York

The principle of exsufflation depends upon inflation of the lungs with a pressure of 40 mm. Hg, i.e., 54 cm. H_2O, with sudden termination of expiration in 0.06 seconds. The device employed, the exsufflator, is attached to the conventional tank respirator.* A negative pressure of 40 mm. Hg is gradually developed in the chamber by a motor blower unit in the period of 2.5 seconds. The swift opening of a five inch butterfly valve results in the pressure surrounding the body of the patient becoming atmospheric in 0.06 seconds.

The physiologic consequences of this procedure are: (1) a two-fold dilatation of the small and medium sized bronchi, (2) a high volume expiratory flow rate approximately equal to that of a moderately vigorous cough in normal individuals and (3) a swift shortening and contraction of the bronchial tree. As a result of the elimination of pressure during expiration, except at the very onset of the expiratory cycle, ventilation is provided at a lower mean pressure than that obtainable with any other supra-atmospheric form of intermittent positive pressure breathing ap-

*This Exsufflator is manufactured by the de Florez, 116 East 30th Street, New York. A portable Exsufflator, employing a mask or mouth-piece and used for IPP and NPP as well as mechanical "coughing," is made by the OEM Corporation, East Norwalk, Connecticut.

paratus. An additional and consequent influence of this type of mechanical ventilation is that a smaller compensatory rise in venous pressure is also secured than obtaniable with methods of mechanical ventilation in which a more gradual pressure curve is present during expiration. The effect of either continuous or intermittent pressure breathing on the cardiac hemodynamics is proportional to the mean applied intrapulmonary pressure. In patients with shock or peripheral circulatory failure, the return of blood to the right heart may be adversely affected by pressure breathing; a principle of mechanical ventilation which is characterized by an exceptionally low mean ventilatory pressure, as mentioned above, may be employed with less hazard.

Exsufflation has been found clinically effective in the elimination of bronchial secretions in syndromas in which an adequately forceful cough is not present. These include poliomyelitis, bronchial asthma, pulmonary emphysema, bronchiectasis, blocked cavities and respiratory depression. Exsufflation has been found superior to the use of respirator in the treatment of respiratory acidosis in patients with pulmonary emphysema. In addition, this mechanism has been shown to relieve obstructive dyspnea under experimental and clinical conditions. Experiments are in progress to achieve a similar purpose with the use of a mask intermittent pressure breathing device.

Intermittent negative pressure breathing refers to the inhalation of atmospheres of air or oxygen under negative pressures of 20 to 40 cm. H_2O initiated at the start of the expiratory cycle. After broncho-dilatation has been accomplished by nebulization of vaponefrin or other broncho-dilator compound, negative pressure breathing has been shown to result, in some cases of emphysema, in a decrease of the functional residual air, manifested by a sharp rise in vital capacity and maximal breathing capacity. The effect is in some respects similar to compression of the lower thorax and manual elevation of the diaphragm in which the gradient of pressure is increased on the chest above that in the respiratory passageway. With negative pressure breathing the gradient of pressure on the chest is increased by lowering the intrapulmonary pressure. The peripheral venous pressure is immediately lowered by respiration under negative pressure, as contrasted to the consistent increase in venous pressure initiated by pressure breathing, whether it is continued or intermittent. Studies are in progress which include the clinical and physiologic effects of intermittent negative pressure breathing (I.N.P.B.) as well as the development of an apparatus whereby both positive and negative pressure breathing may be suitably employed.

Viscero-diaphragmatic breathing is the term employed by Barach, Beck, and Bickerman to describe the use of the head down position for achievement of diaphragmatic respiration. Its effect is like that of pneumoperitoneum except that the weight of the viscera is employed to raise the diaphragm, when the patient is placed head down at an angel of 12 to 20 degrees. In patients with pulmonary emphysema the ventilation is decreased 20 to 30 per cent, without fall in the arterial oxygen saturation

or retention of carbon dioxide, which take place when the anoxic emphysematous patient breathes high concentrations of oxygen.

Viscero-diaphragmatic breathing has been employed both to relieve the dyspnea of patients with pulmonary emphysema and also, surprisingly enough, some patients with bronchial asthma, and, in addition, as a part of the training period to inaugurate diaphragmatic breathing. In some instances the arterial oxygen saturation is elevated, but even in those cases in which the arterial oxygen tension is unchanged, the increased efficiency of this type of abdominal respiration is revealed by maintainance of an equal exchange of oxygen and carbon dioxide in the alveoli in the presence of a sharply decreased minute volume of ventilation.

The dyspnea of some patients who previously required oxygen therapy has been relieved by breathing air in the head down position as described above. This may be employed in various ways, with the use of a so-called glamour board, elevation of the Gatch bed, elevation of the foot of the bed with shock blocks or by especially designed chairs in which the back may be released and inclined to the floor of the room. The effectiveness of viscero-diaphragmatic breathing in producing a more efficient diffusion of oxygen and carbon dioxide in patients with pulmonary emphysema is increased by previous broncho dilatation with nebulized vaponefrin and manual elevation of the diaphragm. The proper use of this procedure results in abandonment of employment of the accessory neck muscles and upper intercostals and the substitution of ventilation of the lower lobes with increased diaphragmatic excursion. The degree of diaphragmatic movement as the result of the head down position was found to be 3.0 cm. higher than that obtained in the sitting position in 20 patients with severe pulmonary emphysema. The demonstration of the value of diaphragmatic breathing under these circumstances is a stimulus to the patient to learn its practice in the sitting, standing and walking postures, in conjunction with the wearing of the low abdominal belt.

CLINICAL USE OF INTERMITTENT POSITIVE PRESSURE BREATHING COMBINED WITH NEBULIZATION IN PULMONARY DISEASE

PETER A. THEODOS, M.D., F.C.C.P.
Philadelphia, Pennsylvania

Intermittent positive pressure breathing (IPPB), as provided by an automatic or patient controlled respirator combined with a nebulizer for the simultaneous administration of bronchodilators, antibiotics and other aerosols, is an effective adjunct to the treatment of many acute and chronic pulmonary conditions where respiratory difficulty or insufficiency is present. These conditions include emphysema, with or without superimposed bronchial infection, silicosis, bronchiectasis, bronchial asthma, pulmonary fibrosis, pulmonary edema, barbiturate poisoning, poliomyelitis and other conditions where dyspnea or impaired movement of the diaphragm is present.

IPPB consists of active inflation of the lungs under positive pressure during inspiration and passive deflation during expiration, produced namely by the elastic recoil of the lungs and chest wall. This type of breathing differs from expiratory positive pressure breathing in which the patient exhales against a positive pressure; and from continuous positive pressure breathing in which the positive pressure is maintained during both phases of respiration. In IPPB the peak mask pressure varies with the line pressure which is adjustable from 0 to 30 cm. of water. When the peak mask pressure is reached (usually set at 20), cycling of the valve occurs and expiration takes place at or about atmospheric pressure. The cycling valve may be pressure sensitive (automatic) or flow sensitive, responding to the patient's own breathing pattern in the latter instance.

Studies have shown that IPPB does not significantly alter cardiac hemodynamics. The cardiac output is usually slightly decreased, the blood pressure in the systemic arteries, right ventricle and pulmonary artery slightly increased, and a moderate degree of hyperventilation produced (6 to 10 liters per minute). It will not produce distention of the lungs even with prolonged application and will not aggravate pre-existing emphysema.

The use of IPPB provides:

1) An efficient means of oxygen (100 per cent) or oxygen-helium (30 to 70 or 40 to 60 per cent) administration.
2) More adequate ventilation of the lungs (increased minute volume and depth of respiration) with no increase in the breathing effort.
3) Promotion of bronchial drainage during the expiratory phase by the high velocity expiratory gas flow produced by the rapid release of inspiratory pressure.
4) A more uniform alveolar aeration with improvement in the respiratory blood gas exchange (arterial oxygen saturation increased).
5) A more effective means for the dissemination of aerosols into the poorly ventilated areas of the lungs with relief of bronchospasm and mucous plugging, and
6) An effective form of deep breathing exercise.

A course of treatment consists of three 20 minute applications of IPPB daily for a period of three to six weeks using 100 per cent oxygen and a bronchodilator drug in the nebulizer. Eight drops of the drug (vaponefrin, isuprel, aerolyn compound, neosynephrine) are diluted with eight drops normal saline and the nebulizer adjusted until a fine spray is visible. The treatment is best given with the patient in the sitting position and either a face mask or mouth piece and nose clip can be used. The number of treatments, the duration of single treatments and the type and quantity of bronchodilator and other drugs may be varied for the individual case. Subjective relief is manifested by lighter and easier breathing, less "tightness" of the chest, decreased cough and expectoration and increased strength.

Contraindications to the use of this form of therapy are few. It should be avoided in recent hemoptysis, spontaneous pneumothorax, and cardiac disease where myocardial ischemia is present. Bronchodilator drugs should

be chosen with care according to the condition of the patient. Vasopressor drugs should be administered with caution in the presence of hypertension, generalized arteriosclerosis and coronary artery disease.

Several apparatuses are commercially available for giving IPPB treatments. The Pneophore* is an automatic, pressure sensitive, cycling device with an instantaneous flow rate of approximately 50 to 60 liters per minute. Several disadvantages of this apparatus have been overcome in the new M.S.A. Pulmonary Ventilator,* which is also pressure sensitive, but follows the patient's pattern of breathing. It has a higher flow capacity than the Pneophore and is easier to clean. The Bennett Pressure Breathing Therapy Unit† has been specifically designed for giving IPPB treatments. It has a flow sensitive valve which follows the patient's own breathing pattern and provides an instantaneous flow rate of well over 100 liters per minute. It is easy to clean and maintain and no rebreathing through the cycling valve occurs. All of these apparatuses have a separately connected nebulizer attachment.

*Manufactured by the Mine Safety Appliances Company, Pittsburgh 8, Pa.
†Manufactured by V. Ray Bennett and Associates, Los Angeles 48, California.

RESPIRATORY ACIDOSIS, INCLUDING THE USE OF INTERMITTENT PRESSURE BREATHING

M. S. SEGAL, M.D., F.C.C.P.
Boston, Massachusetts

The purpose of this communication is to call attention to the increased morbidity and mortality in patients with the so-called "carbon dioxide intoxication syndrome." This syndrome has also been referred to as the "carbon dioxide narcosis syndrome," and "respiratory acidosis." It occurs in patients with chronic hypoxia of long standing, usually secondary to chronic pulmonary emphysema or pulmono-cardiac disease. It rarely, if ever, is seen in uncomplicated bronchial asthma. These patients have evidence of oxygen unsaturation and unfortunately are unable to tolerate sudden administration of high concentrations of oxygen.

Physiologic Mechanism

In these patients, the medullary respiratory center has become insensitive to carbon dioxide. The so-called centrogenic drive for respiration has been lost. The drive for respiration is maintained by the chemoreflex centers located in the carotid and aortic bodies. The drive for respiration which originates in these centers depends upon the hypoxic stimulus. If this stimulus is suddenly removed by the administration of high concentrations of oxygen, the sustaining drive for respiration in these patients is lost, and a reduction in total pulmonary ventilation may follow. These patients complain of somnolence, irritability, headaches, confusion, personality changes, and ultimately with further depression of respiration, coma and death may ensue.

In an arterial blood sample obtained from a patient with severe chronic hypoxic emphysema, the following may be found: elevated pCO_2 (tension), elevated CO_2 content, lowered serum chlorides, and a normal or slightly lowered pH. If high concentrations of oxygen are inadvertently employed, the pCO_2 and CO_2 content will increase and actually a severe degree of respiratory acidosis (lowered pH) may follow. The patient attempts to compensate (maintain a normal pH) by developing a metabolic alkalosis, characterized by a further increase in CO_2 content, increased buffer base content, and lowering of the serum chlorides. If the compensation is not adequate, respiratory acidosis with a drop in pH follows. The course of this syndrome may be followed by obtaining venous blood samples (anaerobically) and testing for CO_2 content, chlorides, and pH. It should be stressed that the pCO_2 which is obtained indirectly from the pH and CO_2 content, applying the Singer-Hastings normogram, is the critical value for determining the degree of respiratory acidosis.

*Treatment**

A. *Prevention.* Prevention is the best treatment.

1) The physician should be aware of the increased incidence of this syndrome in patients with chronic hypoxia secondary to chronic pulmonary emphysema and pulmono-cardiac disease.
2) Do not employ respiratory depressing drugs which may reduce the pulmonary ventilation in the hyperventilating patient, i.e., morphine, barbiturates, and depressing anesthetic agents.
3) Do not employ high concentrations of oxygen in such patients.
4) Avoid particularly the combination of 2 and 3.
5) Employ graduated oxygen therapy, starting with one liter of oxygen per minute. This should be increased by one liter flow daily until six liters per minute has been reached.

B. *Actual Treatment.* If this syndrome occurs and there is evidence of depressed respirations and respiratory acidosis, the following measures should be instituted:

1) Intermittent positive pressure breathing inspiratory.
2) Emergency pneumoperitoneum
3) The use of respiratory chambers.
4) The use of a program of graduated oxygen therapy to correct the hypoxia.

*From Segal, M. S. and Dulfano, M. J.: "Chronic Pulmonary Emphysema—Physiopathology and Treatment," April 1953, Grune and Stratton, Inc., New York.

Editorial

The first of a series of short articles on teaching chest disease appears in this issue of the Journal. These essays are sponsored by the Committee on Undergraduate Education of the American College of Chest Physicians and are intended to stimulate an interest in the problems of effective teaching in this branch of medicine by an exchange of ideas.

It has long been a cardinal objective of the College to improve undergraduate and graduate training in diseases of the chest. Numerous efforts have been constantly active through the years and there have been noteworthy accomplishments. The post-graduate seminars which are held in various parts of the country are among the outstanding results of these efforts.

Interest has recently become more intense about undergraduate teaching problems for several reasons. Changes which are rapidly occurring in the medical school curriculum demand that we reconsider our teaching methods in the light of these changes and our ideal of adequate training. Each year sees the amount of material to be taught medical students increase impossibly. What was once an adequate four year course now contains enough material to require five or six years of undergraduate study. To maintain the four year curriculum there will continue to be a tremendous amount of pushing and shoving and, like growing birds in a nest, something has to give.

Chest disease, which once enjoyed the luxury of time for leisurely undergraduate study is now finding that time shortened in many schools, with undesirable results. Students are not adequately presented the problems and techniques of this field and, therefore, cannot become familiar with them or even interested in them.

Suggestions to remedy this growing deficiency have been made through the medical college deans. While warmly received and accepted, they have lacked fulfillment largely as a result of local problems of organization. A recent questionnaire by the Committee on Undergraduate Education revealed many such areas in which effective teaching of chest disease has been hindered. The Committee feels that the solution for many of these local problems may be reached more effectively through a concerted interest and effort by the members of the College who are actually doing much of the teaching of chest disease throughout the country.

We cannot recapture much time in undergraduate teaching under the present trend of streamlined curricula. However, efforts in this direction should continue, especially in those schools where the time allotted is grossly disproportional to the importance of the field.

Whether or not we can obtain more time, we certainly can make more effective use of the time already allotted to chest disease. Coordination of lectures, clinics and out-patient services; improvement of teaching methods; increase in rapport between sanatoria and general teaching hospitals; exchange of colorful and useful teaching material; exchange of successful teaching personnel on the undergraduate level; invitation of

undergraduates to attend local society meetings and courses; invitation of undergraduates to share in clinical and research projects, mass surveys, etc., all would help increase student interest in chest disease.

It is amazing how much can be accomplished by simply coordinating the group who already do the teaching. A coordinated program designed by the men who do the teaching in each community will produce more favorable action by their dean and executive committee than any other approach. The Board of Regents of the American College of Chest Physicians voted at the last annual meeting that each chapter include a discussion of undergraduate teaching of chest disease in their meetings this year in an attempt to provide leadership to the production of a coordinated teaching program.

This new series of articles on teaching chest disease is another approach to the problem. An exchange of methods, ideas, and suggestions should be stimulating to anyone seriously concerned with the effectiveness of his own teaching. Strangely enough, this concern has been conspicuous by its absence in medical education. Having grown from a preceptorship method, medicine still holds that any M.D. is, by virtue of that degree, a competent teacher.

The primary and secondary schools, and many colleges have long since abandoned the idea that training in a field makes a teacher of that subject and now require training in education. We would not consider sending our children to a school of amateur teachers. Yet we must recognize that most physicians teaching in medical schools are amateur teachers, untrained in methods of education or even in public speaking. Our medical knowledge must be supplemented with methods of effectively presenting that knowledge to others.

This new series of articles is a beginning in that direction, by providing a forum for ideas about methods of teaching chest disease. We, therefore, welcome contributions by everyone who is interested.

The importance of this venture can be measured in terms of the relationship between the undergraduate teaching today and the practice in the field of chest disease tomorrow. The future of the American College of Chest Physicians will be determined in a large measure by the success or failure of our current teaching of chest disease to medical students.

Edward W. Hayes, M.D.
Theodore H. Noehren, M.D.

Interim Session

The interim session of the College will be held at the Hotel Sheraton, St. Louis, Missouri, on Sunday and Monday, November 29 and 30, 1953. On Sunday, November 29, the Missouri Chapter of the College will sponsor a scientific program and on Monday, November 30, the Board of Regents will hold its semi-annual meeting. The Clinical Meeting of the American Medical Association will be held in St. Louis during the dates December 1 through 4.

The Committee on General Arrangements for the interim session of the College, comprising Dr. Alfred Goldman, Dr. A. J. Steiner and Dr. Edward Dunner, all of St. Louis, has announced the following program:

SUNDAY, NOVEMBER 29:

Morning Session

Herbert L. Mantz, Kansas City, Missouri, Chairman
Edward Dunner, St. Louis, Missouri, Secretary

"Current Treatment of Tuberculous Meningitis,"
Eugene J. Des Autels, Chicago, Illinois.

"The Origin and Differential Diagnosis of Pain in the Chest,"
Andrew L. Banyai, Milwaukee, Wisconsin.

"Pulmonary Manifestations of Disseminated Lupus,"
Philip Tumulty, St. Louis, Missouri.

"Mechanical Factors in the Therapy of Chronic Pulmonary Insufficiency,"
Ross Kory, Nashville, Tennessee.

"Isoniazid and Combined Antimicrobial Agents in Treatment of Recent and Acute Forms of Pulmonary Tuberculosis, Preliminary Report,"
David Reisner, Werner Bloch and Antonia Adamsons, New York, New York.

Round Table Luncheons

1) "Cancer of the Lung,"
Lauren Ackerman, St. Louis, Missouri; Alfred Goldman, Beverly Hills, California; and Evarts A. Graham, St. Louis, Missouri.
Moderator: Seymour M. Farber, San Francisco, California.

2) "Pulmonary Function,"
Burgess L. Gordon, Philadelphia, Pennsylvania and Ross Kory, Nashville, Tennessee.
Moderator: Herbert C. Sweet, St. Louis, Missouri.

3) "Management of Pulmonary Tuberculosis,"
Elliott Mendenhall, Dallas, Texas; Eugene J. Des Autels, Chicago, Illinois; and David H. Waterman, Knoxville, Tennessee.
Moderator: Sumner S. Cohen, Oak Terrace, Minnesota.

Afternoon Session

Lawrence E. Wood, Kansas City, Missouri, Chairman
David N. Kerr, St. Louis, Missouri, Secretary

"A Study of Clinical and Cytologic Aspects of Pulmonary Alveolar Adenomatosis,"
Seymour M. Farber, David Wood, George Fuchs and Sam Pharr, San Francisco, California.

"Recent Progress on Histoplasmosis,"
Michael L. Furcolow, Kansas City, Kansas.

"Left Heart Catheterization,"
Alfred Goldman, Beverly Hills, California.

"Scalene Node Biopsy,"
Lawrence M. Shefts, San Antonio, Texas.

Evening Session

Cocktail Party,
Courtesy of the Missouri Chapter, American College of Chest Physicians.

Dinner,
Speaker: Alvis E. Greer, Houston, Texas, President
American College of Chest Physicians.

X-Ray Conference,
William Seaman, Assistant Director, Mallinckrodt Institute of Radiology, Washington University School of Medicine, St. Louis, Missouri.

MONDAY, NOVEMBER 30:

10:00 a. m.: Tour through Barnes Hospital of St. Louis.
2:00 p. m.: Semi-annual Meeting, Board of Regents.

All sessions will be held at the Hotel Sheraton. Reservations for the round table luncheon discussions may be made through the Executive Offices of the College in Chicago. Requests for reservations must be accompanied by remittance in the amount of $3.00 for each luncheon. Please indicate choice by number.

Council on Pan American Affairs

The Council on Pan American Affairs of the College will hold a meeting in conjunction with the Tenth Congress of the Union of Latin American Tuberculosis Societies (ULAST) to take place in Caracas, Venezuela, December 5 through 10, 1953.

The meeting of the Council will be held at breakfast on Thursday, December 10, at 8:00 a.m. Regents and Governors of the College in the Latin American countries, as well as Council members, will gather to discuss the international activities of the College and the program of the College in their respective countries.

The special theme for discussion at the Tenth Congress of ULAST will be "The Organization of Medical and Auxiliary Personnel for the Fight Against Tuberculosis" to which have been invited professors of tuberculosis from all of the Latin American universities and the heads of all the national anti-tuberculosis associations. The above subject will be discussed at a round table forum. In addition, the subject "Anatomic-Pathologic Aspects of Tuberculosis in Latin America" will be discussed by delegates from the various countries.

President of the Tenth Congress of ULAST is Dr. Jose Ignacio Baldo, Caracas, Venezuela, and Dr. Fernando D. Gomez, Montevideo, Uruguay, is Secretary-General. Both Dr. Baldo and Dr. Gomez are Regents of the College. Members of the Organizational Committee are: Drs. Pedro Iturbe, Carlos Ortega G., Alejandro Principe M., R. Valladares G., Luis Gomez Lopez and Julio Criollo Rivas.

Physicians desiring to participate in the program are requested to write to Dr. Jose Ignacio Baldo, Sanatorio Simon Bolivar, El Algodonal, Caracas, Venezuela, and send a copy of the letter to the Executive Offices of the College in Chicago.

Postgraduate Course Presented in Pittsburgh

The Council on Postgraduate Medical Education of the College, with the cooperation of the Pennsylvania Chapter, and the American Academy of General Practice of Western Pennsylvania, presented a Postgraduate Course on Diseases of the Chest, held at the Pittsburgher Hotel, Pittsburgh, on four successive Sundays, beginning September 13. The course was approved for 16 hours of formal credit towards postgraduate education requirements of the Pennsylvania Chapter of the American Academy of General Practice. Officers of the course were Edward Lebovitz and C. Howard Marcy, Co-Chairmen; C. Richard Walmer and Daniel C. Braun, Assistant Secretaries.

Will Rogers Hospital Announces Achievement Awards Program

The Will Rogers Memorial Hospital of Saranac Lake, New York has announced that an annual Achievement Awards Program will be initiated as a stimulus in the fight against tuberculosis and other chest diseases. The first presentation of the annual awards will be made at the 20th Annual Meeting of the American College of Chest Physicians to be held in San Francisco, California, June 17-20, 1954. The nominees for the awards will be selected by the College and a committee of judges representing the College, the American Medical Association and the Medical Staff of the Will Rogers Memorial Hospital will determine the individuals eligible for the awards. Those who have made the greatest discovery in research, the most important medical contribution, and the highest achievement in surgery of chest diseases, in the judges' opinion, will be honored individually each year. Sculptured bronze plaques and cash honorarium will be awarded in each of the three fields. Dr. Edgar Mayer, Regent of the College for New York State and Medical Advisor to the Board of the Will Rogers Memorial Hospital, presented the proposed plan to the Board of Regents of the College at their annual meeting in New York City on May 28, where it was unanimously approved.

College Chapter News

TENNESSEE CHAPTER

The organizational meeting of members in Tennessee was held at the Hotel Peabody, Memphis, April 14. The chapter will sponsor a Chest Disease Section at the Tennessee State Medical Association meeting and a postgraduate course for general practitioners. The officers elected are:

David H. Waterman, Knoxville, President
Duane Carr, Memphis, Vice-President
Hollis E. Johnson, Nashville, Secretary-Treasurer.

MINNESOTA CHAPTER

At the Annual Meeting of the Minnesota Chapter, Hotel St. Paul, May 20, Drs. Herman J. Moersch and Arthur M. Olsen, both of Rochester, were re-elected President and Secretary-Treasurer respectively. Dr. Leo G. Rigler, Minneapolis, discussed his recent trip to India.

OHIO CHAPTER

The following officers were elected at the Ohio Chapter meeting in Cincinnati, April 22:

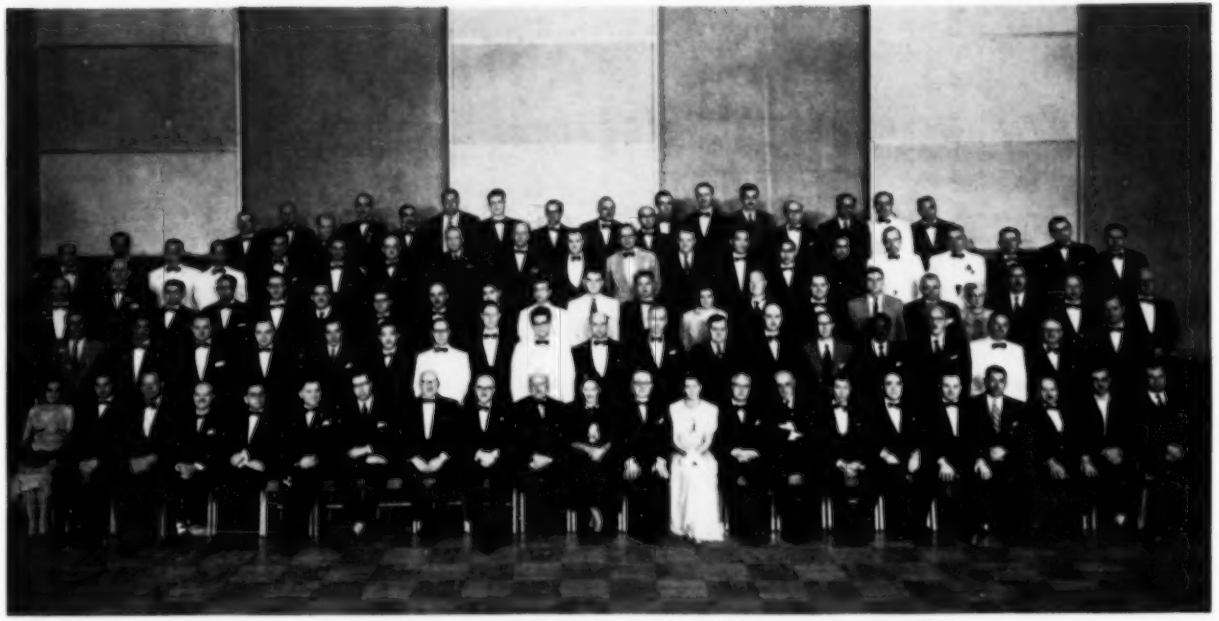
Lynne E. Baker, Dayton, President
James T. Villani, Akron, Vice-President
H. H. Brueckner, Canton, Secretary-Treasurer.

CALIFORNIA CHAPTER

An interesting program was presented at the California Chapter meeting held in conjunction with the California State Medical Association meeting at the Hotel Biltmore, Los Angeles, May 27. The following members were elected to office:

Alfred Goldman, Beverly Hills, President
W. G. Winters, Fresno, Vice-President
W. B. Brown, Livermore, Secretary-Treasurer.

CONVOCATION CLASS, 1953



Members who received Fellowship certificates at Convocation, held at the Hotel New Yorker, New York City, May 30, 1953, in conjunction with the 19th Annual Meeting.

PORTUGUESE CHAPTER

The annual meeting of the Portuguese Chapter was held May 30 and 31 at the Caramulo Sanatorium, Caramulo, Portugal, under the direction of Doctor Celso Horta e Vale, Caramulo, Immediate Past-President of the Chapter. Officers elected for 1953-54 are:

Agostinho Cardoso, Funchal, President
C. Carvalho Dias, Lisbon, Vice-President
Lopo de Carvalho Cancella, Parede, Secretary
Raymundo Quintanilha, Lisbon, Treasurer.

The following program was presented:

"The Moment of Collapse Therapy in the Pathogenesis of Tuberculosis,"
Celso Horta e Vale, Caramulo.

"Metastatic Adenoma of the Thyroid (Interpretation of Nodular Pictures of the Lung),"
Augusto Vaz Serra, Coimbra.

"Tumors of the Thoracic Wall,"
J. R. Bello de Morais, Lisbon.

"Contribution of Tomography to the Study of Volume Alterations and Situation of Pulmonary Cavities,"
Lopo Cancella, Lopo Carvalho Filho and J. Benard Guedes, Lisbon.

"Photographic Record of Bronchoscopic Pictures,"
Lopo de Carvalho Filho, Lisbon.

"Sheathing Periostosis of Thoracic Origin,"
J. Antunes de Azevedo, Coimbra.

"Antibiotics and Collapse Therapy in Cavitary Pulmonary Tuberculosis,"
Trajano Pinheiro, Caramulo.

"Contribution to the Study of the Action Mechanism of Collapse Therapy,"
Jose M. Soares de Oliveira, Caramulo.

"Results of Pneumoperitoneum in the Treatment of Pulmonary Tuberculosis,"
Joao Lacerda, Caramulo.

"Importance of Separated Spirometry in Pneumology,"
Galvao Lucas, Lisbon.

"Prophylaxis and Treatment of Post-operative Atelectases,"
Lopo de Carvalho Filho, Lisbon.

"Considerations on Pulmonary Resections with Immediate Thoracoplasty. Case Report,"
Rui de Lima, Lisbon.

"Considerations on a Course of Tuberculosis Organized by the British Council in England in April,"
Perez Fernandes, Lisbon.

"Value of Sanatorium Recovery in View of the Antibiotic Therapeutics and Modern Chemistry,"
Silva Rosa, Caramulo.

"Some Cases of Cavity Closing Only After the Suspension of the Collapse,"
Lucena e Sampeio, Caramulo.

"Experience with Isonicotinic Acid Hydrazide,"
Julio Vasconcellos, Guarda.

EDITOR'S NOTE

The Portuguese Chapter of the American College of Chest Physicians presents a formidable annual program, covering a large variety of subjects. The authors and officials then arrange to have each paper published in a medical journal and the reprints are brought together in a handsome bound volume which is made available to members of the College and others.

Numbers 1 and 2 of these bound volumes have reached us and they are so impressive as to warrant special consideration. They contain splendid articles in which research projects are reported, practical papers on the latest diagnostic

procedures, as well as most modern treatment, including chemotherapy and resectional surgery. In fact each volume may be likened to a course in diseases of the chest.

The idea of binding these papers together and making the entire annual program available to the members and others can be highly recommended to chapters of the College everywhere.

JAY ARTHUR MYERS, M.D.

COLOMBIA CHAPTER

The first meeting of the Colombia Chapter was held in conjunction with the Second National Convention of Surgeons in Medellin on April 16. Dr. Rafael J. Mejia, Medellin, Governor of the College for Colombia, presented Fellowship certificates to the new members. Dr. Marco Hernandez, Bogota, was elected President; Dr. Eduardo Abad Mesa, Medellin, was elected Vice-President, and Dr. Alfonso Mejia Calad, Medellin, was elected Secretary. Dr. Carlos Arboleda Diaz, Bogota, is Regent for Colombia. The chapter presented the following program:

"41 Lung Resections for Tuberculosis,"
Antonio Ramirez.

"Lung Surgery in War Wounds,"
Jose Pablo Leyva and Manuel de Luca.

"Three Interesting Cases of Thoracic Surgery,"
Augusto Britton.

"Arterio-venous Fistulae in the Treatment of Arterial Hypertension,"
J. T. Henao Triana and E. Echeverri.

"Laryngo-tracheal Stenosis Due to Scleroma,"
Gustavo Gomez Hurtado.

"Coarctation of Aorta. Surgical Treatment,"
Augusto Britton and Sigifredo Demmer.

"Aortic-pulmonary Fistula at the Base of the Heart,"
Antonio Ramirez.

"Some Anesthetic Considerations in Thoracic Surgery,"
Gustavo Scioville S.

"Ductus Arteriosus (Five Operated Cases),"

"Right Transthoracic Esophagectomy,"

"Fallot's Tetrallogy (Surgical Treatment),"

"Aortic Aneurysm (Surgical Treatment),"
Alberto Vejarano, Guillermo Lara and Guillermo Rueda.

"Lung Resection in Children,"
Marco Hernandez.

MICHIGAN CHAPTER

The following were elected officers of the Michigan Chapter on June 24:

Lawrence Pratt, Detroit, President
Forest D. Dodrill, Detroit, Vice-President
William H. Barron, Detroit, Secretary-Treasurer.

FLORIDA CHAPTER

The Florida Chapter met in conjunction with the State Medical Association in Hollywood, Florida, April 26. The following officers were elected:

Nathaniel M. Levin, Miami, President
DeWitt C. Daughtry, Miami, Vice-President
Hawley Seiler, Tampa, Secretary-Treasurer
Jack Reiss, Coral Gables, Program Chairman.

KANSAS CHAPTER

On May 3, in Wichita, members of the College in Kansas met for the first time and formed the Kansas Chapter. Speakers at the meeting were Dr. John Morgan, Emporia, Dr. N. C. Nash, Wichita, and Dr. Alfred Goldman, St. Louis, Missouri, Regent. The following officers were elected:

Charles Pokorny, Halstead, President
A. L. Ashmore, Wichita, Vice-President
Carl J. W. Wilen, Manhattan, Secretary-Treasurer
Andre Baude, Topeka, Program Chairman.

NEW ENGLAND STATES CHAPTER

At the New England Deaconess Hospital, Boston, Massachusetts, May 20, members of the New England States Chapter elected the following officers:

Hubert Boyle, New Bedford, Massachusetts, President
Frank Merlino, Providence, Rhode Island, Vice-President
John B. Andosca, Boston, Massachusetts, Secretary-Treasurer.

Dr. James Walker, Brookline, Massachusetts and Dr. Wilford B. Neptune, Philadelphia, Pennsylvania, spoke on "Revascularization of the Heart."

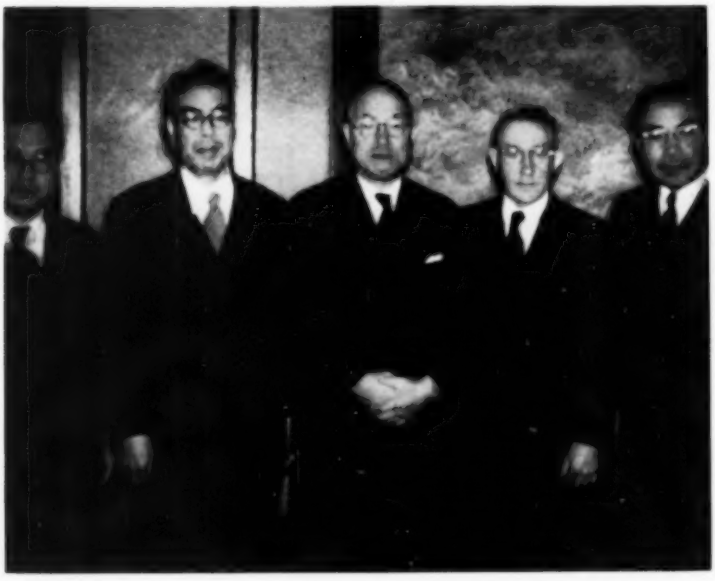
GEORGIA CHAPTER

The following officers were elected at the meeting of the Georgia State Chapter at the Hotel De Soto, Savannah, May 13:

John Elliott, Savannah, President
Joseph S. Cruise, Atlanta, Vice-President
C. W. Mills, Atlanta, Secretary-Treasurer
Bernard Wolff, Atlanta, Program Chairman.

The next meeting of the chapter will be held at the Battey State Hospital, Rome, Georgia, in October, 1953.

JAPAN CHAPTER



Chapter officers (left to right): Shinobu Miyumoto, Naoji Kawai, Hidejiro Haruhi, R. K. Start (Regent), and Jo Ono (Governor).

The inauguration of the Japanese Chapter took place on January 6 in Tokyo. Dr. Leon Unger of Chicago, Illinois, spoke on "Bronchial Asthma" and presented Fellowship certificates to the new Fellows. The following officers were elected:

Hidejiro Haruki, Tokyo, President
Naotsugu Kawai, Chiba City, Vice-President
Shinobu Miyamoto, Tokyo, Secretary-Treasurer.

SOUTH AFRICA CHAPTER

The Northern Chapter of South Africa met May 26 at the Springkell Sanatorium, Transvaal, and elected the following officers:

L. Fatti, Johannesburg, President
J. K. Bremer, Pretoria, Vice-President
W. S. Linton, Transvaal, Secretary-Treasurer.

Past-President Maurice A. Pringle spoke on "The First 50 Pulmonary Resections Carried Out at Springkell Sanatorium."

TEXAS CHAPTER

At the annual meeting of the Texas Chapter held at the Shamrock Hotel, Houston, April 27, it was unanimously resolved that a "Charles M. Hendricks Lecture" be established to be given annually at the meeting of the chapter. The following officers were elected at this meeting:

Henry Hoskins, San Antonio, President
Howard E. Smith, Austin, First Vice-President
Samuel Topperman, Tyler, Second Vice-President
Walter C. Brown, Corpus Christi, Secretary-Treasurer.

MISSOURI CHAPTER

The Missouri Chapter met at the Hotel President, Kansas City, April 25 and elected the following officers:

Lawrence E. Wood, Kansas City, President
George Hobbs, Mount Vernon, Vice-President
David Nafe Kerr, St. Louis, Secretary-Treasurer.

Speakers were: Drs. Karl H. Pfuetze, Chicago, Illinois, "The Chemotherapy of Tuberculous Meningitis"; David B. Radner, Winfield, Illinois, "Prevention of Post-operative Bronchopulmonary Complications"; and John H. Mayer, "Surgical Treatment of Lung Abscess." Dr. Lawrence E. Wood presided over an x-ray conference.

NEW JERSEY CHAPTER

The New Jersey Chapter met at the Haddon Hall Hotel, Atlantic City, May 20, and elected the following officers:

J. Earle Stuart, Plainfield, President
Irving J. Selikoff, Paterson, President-Elect
William C. Douglass, Bernardsville, Vice-President
Samuel Cohen, Jersey City, Secretary-Treasurer (re-elected).

Dr. William C. Douglass was also elected Chairman of the Section on Chest Diseases of the New Jersey State Medical Society and Dr. Lewis F. Baum, South Orange, was elected Secretary of the Section.

SOUTHERN STATES CHAPTER

The Southern Chapter of the College, which comprises the 16 Southern states and the District of Columbia will meet jointly with the Southern Medical Association in Atlanta, Georgia, October 25-26, at the Henry Grady Hotel. The following program will be presented:

MORNING SESSION, OCTOBER 25:
John H. Seabury, New Orleans, Louisiana, presiding.

"Respiratory Alkalosis,"
Bernard P. Wolff, Atlanta, Georgia.

"Bronchitis,"
Dean B. Cole and associates, Richmond, Virginia.

"Observation on the Combined Use of Aldinamide and Isonicotinic Acid Hydrazide on Far Advanced Pulmonary Tuberculosis,"
Arthur Calix, Maurice Campagna and George Hauser, New Orleans, Louisiana.

"Non Surgical Treatment of Carcinoma of the Esophagus,"
Foster Hampton, Chattanooga, Tennessee.

Luncheon Meeting: Regents, Governors, Chapter Officials.
Alvis E. Greer, Houston, Texas, President, American College of Chest Physicians, presiding.

Afternoon Session:
Joseph S. Cruise, Atlanta, Georgia, presiding.

"Differential Diagnosis of Infectious Diseases of the Lungs,"
Thomas Haltam, Nashville, Tennessee.

"Pulmonary Manifestations of Nocardiosis,"
J. Winthrop Peabody, Jr., Oteen, North Carolina; John H. Seabury and Howard A. Buechner, New Orleans, Louisiana.

"Lipoid Pneumonia,"
Fred H. Aves, Houston, Texas.

"Prolonged Isonicotinic Acid Therapy,"
Dan Jenkins, Houston, Texas.

Evening Session:

Social Hour.

President's Banquet,
Dean B. Cole, Toastmaster.

Address: Duane Carr, Memphis, Tennessee, President, Southern Chapter, American College of Chest Physicians, "The Physician of Today."

X-Ray Conference.
R. Kyle Brown, Greenville, South Carolina, Moderator.

MORNING SESSION, OCTOBER 26:

George R. Hodell, Houston, Texas, presiding.

"Chemical Tissue Factors which May be Related to Host Resistance to Tuberculosis,"
Martin M. Cummings, Margaret C. Drummond, Paul C. Hudgins, and Walter L. Bloom, Chamblee, Georgia.

"Differential Diagnosis and Treatment of Pulmonary Hemorrhage,"
Andrew L. Banyai, Milwaukee, Wisconsin.

"Treatment of Tuberculosis in the Mentally Ill,"
George N. J. Sommer, Trenton, New Jersey.

Business Meeting and Luncheon:

Report of Committees.

Election of Officers.

Guest Speaker: "The Surgery of Stenotic Valvular Diseases, Indications and Results," Thomas J. E. O'Neill, Philadelphia, Pa.

INDIANA CHAPTER

The meeting of the Indiana Chapter will be held in conjunction with the Tuberculosis Control Division of the Indiana State Board of Health at the French Lick Springs Hotel, French Lick, October 20. The chapter will present the following program:

"Pneumoperitoneum and Its Complications,"
Otto L. Bettag, Director, Illinois Department of Public Welfare, Chicago and Springfield.

"Out-patient Treatment with Chemotherapy" — General Discussion.

X-Ray Conference.

NORTH CAROLINA CHAPTER

The North Carolina Chapter will meet jointly with the Veterans Administration in Oteen, October 16. The evening session and banquet will be held in Asheville. Dr. Otto C. Brantigan, Baltimore, Maryland, will speak on "Mediastinal Tumors." An X-Ray Conference and panel discussion will follow.

ARGENTINE CHAPTER

The Argentine Chapter held three meetings in July in Buenos Aires, Tucuman, and Salta, and in Mendoza on August 13. Their Annual Meeting will be held November 14 in Mar del Plata with the theme "Chronic Pneumonitis."

College News Notes

Dr. Benjamin M. Gasul, Chicago, Illinois, Chief of Pediatric Cardiology, Clinic Research Hospital, University of Illinois, delivered a series of three lectures at the City of Hope, Duarte, California and the Cedars of Lebanon Hospital, Los Angeles, on "Recent Advances in Pediatric Cardiology" during the first week of September.

Dr. Nathaniel E. Reich, Brooklyn, New York, Associate in Medicine, State University of New York College of Medicine, addressed the National Heart Institute in Mexico City, August 18, on "Newer Methods of Treatment of Heart Diseases."

Dr. Meyer R. Lichtenstein, Chicago, Illinois, has been appointed Medical Director of the City of Chicago Municipal Tuberculosis Sanitarium, an institution of 1,500 beds.

The Rome (Italy) Surgical Society conferred an Honorary Fellowship upon Dr. Charles P. Bailey, Philadelphia, Pennsylvania, Professor of Thoracic Surgery, Hahnemann Medical College.

Dr. Ivan Baronofsky, Assistant Professor of Surgery, University of Minnesota Medical School, spoke on cancer at the Fifth Physicians' Seminar Session, April 28, at the Atlantic Hotel, Marshall, Minnesota.

A citation for distinguished service to the Alumni Association of the University of Kansas has been awarded to Dr. Brian Blades, Professor of Surgery, George Washington University School of Medicine, Washington, D. C.

Dr. J. Arthur Myers, Minneapolis, Professor of Medicine and Public Health, University of Minnesota, was the principal speaker at the Lyon County (Minnesota) accreditation program, April 20.

Dr. Daniel L. Finucane, Superintendent of the Glenn Dale Sanatorium, Maryland, addressed the 51st Annual Meeting of the District of Columbia Tuberculosis Association, May 4, on "The Changing Concepts in the Treatment of Tuberculosis Since the Introduction of the Antituberculosis Drugs." Dr. J. Winthrop Peabody, Washington, D. C., Professor of Diseases of the Respiratory System, Georgetown University School of Medicine, was elected at this meeting to serve on the Association's Board.

Dr. Fred W. Wittich, Minneapolis, Minnesota, as President of the International Association of Allergy, opened the Second European Congress on Allergy held in Copenhagen, Denmark, May 20. He also attended and spoke at meetings of the French Allergy Society in Paris and the Netherlands Society of Allergy in Utrecht. Dr. Wittich has been made a life-time honorary fellow of the Netherlands Society of Allergy.

Dr. Richard A. S. Cory, Director of the King George V Jubilee Memorial Sanatorium, Liguanea, Jamaica, was made an Officer of the Most Excellent Order of the British Empire (Civil Division) by Her Majesty, Queen Elizabeth II.

Dr. Louis L. Friedman, Birmingham, Alabama, and Dr. Louis Mark, Columbus, Ohio, spoke at the Annual Meeting of the Eighth District Medical Society of Ohio at the Rocky Glen Sanatorium, McConnelsville, Ohio, on August 27.

Dr. J. J. Kirshner has been appointed acting Medical Director of the Eagleville Sanatorium, Montgomery County, Pennsylvania.

Obituaries

FRANK R. FERLAINO
1900 - 1953

The passing of Dr. Frank R. Ferlaino at the peak of his career has infused a sense of real sadness into those of us who worked with him and knew him well. Dr. Ferlaino died on September 3, 1953 after an illness of several days. His admirable professional ability, sympathy and optimism made him greatly beloved as a physician. He gave ever freely of his time and energy and displayed keen interest in his fellow-man whether of high or low station, rich or poor, regardless of race or creed.

Dr. Ferlaino achieved distinctive athletic honors during his college years. At Princeton University he was a four-letter man, excelling in baseball, football, lacrosse and wrestling. He was an All-American lacrosse player. He pursued his interest in athletics and served creditably as Chairman of the Advisory Board of the New York State Athletic Commission, 1948-1950, by appointment of Governor Thomas E. Dewey. In this capacity he endeavored to improve standards for the physicial examination of boxers and wrestlers.

Dr. Ferlaino was born in New York City and served in the Navy during World War I as Seaman First Class. He graduated from Princeton in 1922 with a B.S. degree and received his M.S. from that institution the following year. He received his degree of Doctor of Medicine from Johns Hopkins University in 1927 and then served as an interne and resident physician at the Columbia-Presbyterian Medical Center. He later pursued postgraduate studies at Columbia University.

Dr. Ferlaino had practiced medicine in New York City since 1930. He was a staff physician at Roosevelt Hospital and attending physician at the University Hospital of the New York University-Bellevue Medical Center. He was deeply interested in industrial medicine and served as assistant clinical professor of industrial medicine at the Center's Institute of Industrial Medicine. He was clinical instructor in industrial medicine at the New York Medical College-Flower and Fifth Avenue Hospitals and has served on the staff of Kings County Hospital.

Dr. Ferlaino had been a director of the American Research and Education Foundation and a director and Secretary of the Common Cold Foundation. He had been actively concerned in organizing a research project on the prevention and cure of the common cold, a well-recognized impediment to industrial productivity. Dr. Ferlaino was associate editor of the Journal of Industrial Medicine; he was district counselor for the Industrial Medical Association in Southern New York and Northern New Jersey; he served on the Industrial and Health and Accident Prevention Committee of the New York State Medical Society; and was coordinator of the American Symposium on Industrial Medicine and Surgery, 1943-1946. Since 1945 Dr. Ferlaino had served in New York as Medical Director for General Motors Company and was for many years actively affiliated with numerous companies as an outstanding insurance consultant.

His active participation in affairs of the American College of Chest Physicians, and particularly his efficient cooperation, as Secretary of the Council on Postgraduate Medical Education and Co-Chairman of the annual Postgraduate Course in Diseases of the Chest presented in New York City, brought us into close contact and led to the development of a personal friendship and my increasing appreciation of his great inner zeal, limitless drive and many talents.

The sudden passing of Dr. Ferlaino is a grievious shock to his many friends and associates. His transit from the tossing tempest to the harbor-haven of continual ease in the World to come is felt not only as a distinct personal loss to those of us who knew him intimately, but also to the cause of medicine to which he was so creditably and energetically devoted.

EDGAR MAYER, M.D., Regent for New York State.

A. H. BAKER

1883 - 1953

On July 31, 1953, in Shaughnessy Hospital, Vancouver, B. C., Dr. A. H. Baker died of coronary thrombosis.

Dr. Baker was widely known throughout Canada for his work in the field of tuberculosis, and will be especially missed in the Province of Alberta, where he directed the fight against this disease for 32 years.

Dr. Baker was a Fellow of the American College of Chest Physicians, a Fellow of the Royal College of Physicians of Canada, a member and past president of the Canadian Tuberculosis Association and of the Calgary Medical Society, a member of the Canadian Medical Association, one of the founders and for many years a director of the Alberta Tuberculosis Association, and a former member of the Calgary Rotary Club. He was on the consultant staff of the Calgary General Hospital and the Colonel Belcher Hospital.

Surviving are his son, Dr. Perren E. Baker, Edmonton; a sister, Mrs. J. R. Wright, Vancouver; two brothers, P. E. Baker, Vancouver, and A. G. Baker of Portland, Oregon; and two grandchildren.

We who are left will miss him. He was one of the few who really reach the peak of greatness. He will be remembered as a true physician, a loyal friend and an able teacher.

L. M. MULLEN, M.D., Governor for Western Provinces.

Book Reviews

THE BRITISH JOURNAL OF TUBERCULOSIS AND DISEASES OF THE CHEST.

Nineteen hundred and fifty-two was the forty-sixth year of publication of the British Journal of *Tuberculosis and Diseases of the Chest.** It was considerably increased in size and to its already efficient Editorial Board, consisting of Phillip Ellman, Editor, and Charles Cameron, Clifford Hoyle, A. Brown Taylor, E. Holmes Sellors as members, were added four widely known experts in diseases of the chest, consisting of B. A. Dormer, Durban, South Africa; Cotter Harvey, Sydney, Australia; Hugh E. Burke, Montreal, Canada; and F. H. Smirk, Otago, New Zealand. Each of the four 1952 issues were outstanding in its content. In addition to carrying excellent articles, the January issue celebrated the eightieth birthday of Sir Robert Young of world-wide renown as physician and teacher. With this splendid array of editorial board members known everywhere for the excellence of their work and contributions in the field of diseases of the chest including tuberculosis there can be no doubt about the continued high quality of this Journal.

*Published by Bailliere, Tindall & Cox, Ltd., 7-8 Henrietta St., London 1, W. C.

British physicians have long played an exceedingly important role in every phase of medicine. Their discoveries have added tremendously to the span of human life. When Edward Jenner presented a successful method of vaccination against smallpox in 1796, it was said that he added four years to man's life. When Sir Alexander Fleming discovered penicillin in 1928, he initiated work which has resulted in chemotherapy so effective against infections it is believed to have increased the span of human life by ten years.

Some of the early attempts to control tuberculosis began in England. Thomas Beddoes, Shropshire, in his Essay on Consumption, 1803, strongly recommended research in tuberculosis by physicians and advocated organization for such an undertaking. It was George Sutton of Colfield who is credited with attempting to operate the first sanatorium in the world and who, in 1840, wrote "The Treatment and Cure of Pulmonary Consumption." It was Thomas Southwood who participated so effectively in the Health of Towns Association in England in 1844, in an attempt to enlighten the public for the purpose of improving sanitation and which played an important role in establishing the General Board of Health in England in 1848. It was William Budd, Devonshire, who contributed so effectively to our knowledge of epidemiology of tuberculosis. If space permitted, a long list of more recent British physicians and scientists who have made outstanding contributions in the field of diseases of the chest could be added, including Sir Robert Philip, Edinburgh; A. Stanley Griffith, Cambridge; and Sir Robert Young, London.

Current British workers are contributing so much to our knowledge in this field that one may expect a large number of excellent articles to appear regularly in British publications including the British Journal of *Tuberculosis and Diseases of the Chest*. Thus, each physician regardless of residence in the world should avail himself of the opportunity to read every issue of this Journal.

J. ARTHUR MYERS, M.D.

WEG, ZIEL UND GRENZEN DER STREPTOMYCINTHERAPY, by Hennenberg, G., Berlin, 1953, W. de Gruyter & Co. (287 pages).

Following a detailed discussion of the basic microbiologic principles of streptomycin therapy, carefully documented and well illustrated text is presented in this book on various phases of antibiotic treatment of tuberculosis and non-tuberculous diseases. Numerous roentgenograms, diagrams, graphs and tables selected with a critical eye and compiled with accuracy and meticulous care, aid in the elucidation of the text.

Streptomycin used in the treatment of tuberculous meningitis is discussed at great length. Detailed presentation is given of the diagnosis, differential diagnosis, chemical and cytological aspects of this condition in children, adolescents and adults. Commendable attention is devoted to the effect of streptomycin upon the eyes, the eighth nerve and the endocrine system. Assaying of the various methods of administration of this drug are creditably handled.

Streptomycin treatment of pulmonary tuberculosis of other organs is covered in 71 pages. Here again the problem is analyzed separately in various age groups. Pertinent data are offered relative to dosage, side-effects and to combination of streptomycin with chemotherapeutic agents. There is a good exposition of the effect of streptomycin upon bronchogenous tuberculosis and tuberculous cavities. Of particular interest are chapters on laboratory investigations, and on the preoperative and postoperative use of streptomycin.

The book contains a concise bibliography and a good index.

ANDREW L. BANYAI, M.D.

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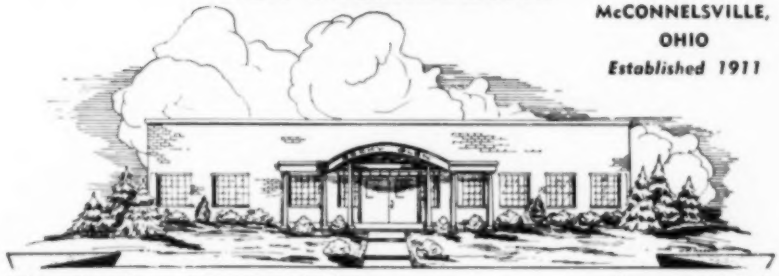

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COLLEGE EVENTS

NATIONAL AND INTERNATIONAL MEETINGS

Interim Session and Semi-Annual Meeting, Board of Regents, Sheraton Hotel, St. Louis, Missouri, November 29-30, 1953.

20th Annual Meeting, American College of Chest Physicians, San Francisco, California, June 17-20, 1954.

Third International Congress on Diseases of the Chest
American College of Chest Physicians
Barcelona, Spain, Fall, 1954

Tenth Congress of the Union of Latin American Societies Against Tuberculosis, Caracas, Venezuela, December 5-10, 1953.

Council on Pan-American Affairs, Caracas, Venezuela, December 10, 1953.

POSTGRADUATE COURSES

6th Annual Postgraduate Course on Diseases of the Chest, Hotel New Yorker, New York City, November 2-6, 1953.

CHAPTER MEETINGS

Southern Chapter, October 25-26, Henry Grady Hotel, Atlanta, Georgia.
North Carolina Chapter, October 16, Veterans Hospital, Oteen, North Carolina.
Indiana Chapter, October 20, French Lick Springs Hotel, French Lick, Indiana.

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Staff physician wanted for sanatorium. Maintenance for family available. State qualifications. Apply to: Dr. Edward A. Favis, White Haven, Pennsylvania.

ANNOUNCEMENT

Applications for grants from the James Picker Foundation for Radiological Research, headed by the Mutual Security Director Harold E. Stassen, may now be submitted for next year. In the past three years, funds totalling $80,000 have been made available to mature investigators to further broaden the uses of radiology for the good of mankind. Awards of grants, fellowships, and scholarships are given in support of a specific research program under the direction of a responsible investigator. Any project offering promise of improvement or development in radiological methods of diagnosis or treatment of disease is eligible for assistance from the Picker Foundation. Applications for grants-in-aid and fellowships should be directed to: James Picker Foundation, Inc., Hanover Bank Trustee, 70 Broadway, New York 4, New York, or Secretary, Division of Medical Science, National Research Council, 2101 Constitution Avenue, N. W., Washington 25, D. C. Final applications should be submitted no later than November 30, 1953.

20th ANNUAL MEETING

The 20th Annual Meeting of the American College of Chest Physicians will be held in San Francisco, June 17-20, 1954. Physicians interested in presenting scientific papers on any phase in the diagnosis and treatment of heart and lung disease should send a 100-word abstract, no later than January 1, 1954, to Dr. Edgar Mayer, Chairman, Committee on Scientific Program, 850 Fifth Avenue, New York 21, New York.

MEDICAL BOOK SERVICE DEPARTMENT

American College of Chest Physicians

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THE CHEST AND THE HEART, J. A. Myers, M.D. and C. A. McKinlay, M.D. and associates; 2 volumes; 1856 pages; 1003 illustrations	$25.50
TUBERCULOSIS AS IT COMES AND GOES, Edward W. Hayes, M.D.; 228 pages; 96 illustrations	4.50
RADIATION AND CLIMATIC THERAPY OF CHRONIC PULMONARY DISEASES, INCLUDING ALL FORMS OF TUBERCULOSIS, Edited by Edgar Mayer, M.D.; 406 pages; 46 figures	5.00
DISEASES OF THE CHEST, Eli H. Rubin, M.D.; 685 pages; 355 figures	14.50
PNEUMOPERITONEUM TREATMENT, A. L. Banyai, M.D.; 376 pages; 74 illustrations	7.50
DIAGNOSIS AND TREATMENT OF CHRONIC DISEASES OF THE RESPIRATORY TRACT, E. H. Funk, M.D., revised by Burgess Gordon, M.D.; 645 pages; 182 illustrations	8.00
ARTIFICIAL PNEUMOTHORAX IN PULMONARY TUBERCULOSIS, T. G. Heaton, M.D.; 292 pages	4.50
SURGICAL EXTRAPLEURAL PNEUMOTHORAX, Donato G. Alarcon, M.D.; 298 pages	8.00
THE TECHNIQUE OF PULMONARY RESECTION, R. H. Overholt, M.D. and L. Langer, M.D.; 224 pages; 122 illustrations	8.00
THE FUNDAMENTALS OF PULMONARY TUBERCULOSIS AND ITS COMPLICATIONS, Sponsored by the American College of Chest Physicians; 492 pages; 219 illustrations	9.50
THE MANAGEMENT OF THE PATIENT WITH SEVERE BRONCHIAL ASTHMA, Maurice S. Segal, M.D.; 168 pages; 24 illustrations	3.50
DISEASES OF THE AORTA, Nathaniel E. Reich, M.D.; 288 pages; profusely illustrated	7.50
RADIOLOGIC EXPLORATION OF THE BRONCHUS, S. De Rienzo, M.D.; 348 pages; 520 illustrations	10.75
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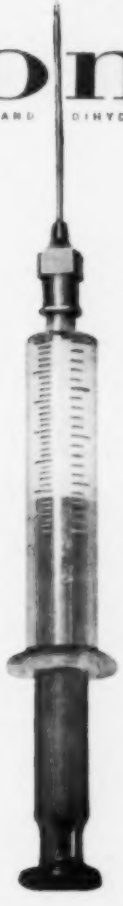

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1. Heck, W. E.: Reduced Ototoxicity by Combined Streptomycin-Dihydrostreptomycin Treatment of Tuberculosis, Scientific Exhibit 317, 102nd Annual Meeting A.M.A., New York, June 1-5, 1953.

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